

# Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers

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Title: INDIVIDUAL PATIENT DATA META-ANALYSIS OF THE RANDOMISED EORTC AND CHORUS TRIALS COMPARING NEOADJUVANT CHEMOTHERAPY VERSUS UPFRONT DEBULKING SURGERY IN ADVANCED TUBO-OVARIAN CANCERS

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**Abstract:** Background. Two prospective randomised trials, comparing neoadjuvant chemotherapy (NACT) with upfront debulking surgery (UDS) in advanced tubo-ovarian cancer (EORTC 55971 and MRC CHORUS) , were analysed with the aim to examine the long term outcomes of the patients and identify any preferable therapeutic approaches for subgroup populations.

**Methods.** Pre-planned individual updated patient data meta-analysis of both trials (NCT00003636 and ISRCTN74802813). In the EORTC trial eligible women had biopsy proven stage IIIC or IV invasive epithelial tubo-ovarian carcinoma. In the CHORUS, trial the inclusion criteria were similar, but women with apparent stage IIIA and IIIB were also eligible. The main aim of the meta-analysis was to show non-inferiority in overall survival with NACT compared UDS using the "reverse Kaplan-Meier" method. Test for heterogeneity was based on the Cochran's Q heterogeneity statistic.

**Findings.** 1220 women were randomised. The overall median follow-up was 7.6 years (EORTC 9.2 and CHORUS 5.9 years). Median patient age was 63 years (range 25-88 years) and median size of the largest metastatic tumour at diagnosis was 8 cm (range 0-50 cm). FIGO stage distribution was II-IIIB(4.5%), IIIC(68.1%), IV(18.9%) with 8.5% of data missing. There was no statistically significant difference for the entire population regarding the median overall survival (OS) between patients who underwent UDS and NACT (26.9 and 27.6 months; HR: 0.98, 95% CI: 0.87-1.10; p = 0.688). Median OS for EORTC and CHORUS patients was significantly different at 30.2 and 23.6 months, respectively (HR: 1.20, 95% CI:1.06-1.36;p=0.004) but not significantly heterogeneous (Cochran's Q p= 0.17). Variable outcomes were noted in some cohorts.

Interpretation. Long-term follow-up data confirm that NACT and UDS result in similar OS in advanced tubo-ovarian cancer, with preferential outcomes in some patients. This meta-analysis, with long-term follow-up, confirms that NACT is a valuable treatment option for patients with Stage IIIC-IV tubo-ovarian cancer, especially in patients with a high tumour burden at presentation and/or poor performance status.

Leuven, July the 13<sup>th</sup>

Dear Senior Editor, Dear Dr Lai,

On behalf of the co-authors, I thank you for your decision to revise our paper and will answer the 3 questions below:

1. Editorial comment 8: thank you for providing the study selection flowchart. To conform to reporting standards, a figure like this is required in the main manuscript. Please could you add the figure to the main manuscript? As the two studies were prospectively selected for inclusion, the boxes on 'records excluded' and 'other studies...' can be removed from the figure.

I have adapted the figure as requested to the main manuscript. The figure numbers and references have been adapted.

2. Editorial comment 11: thank you for providing figure files. Unfortunately, the .doc files you have provided for your figures are not editable. The graphs are images and cannot be edited. Please could you provide editable files for all of your graphs and figures—eg, .eps, .ps or .pdf files saved directly from the original artwork or plotting device so we can reformat the original drawing. Please note that the text and drawings will need to be editable. If you have any questions about this, please do not hesitate to contact me directly.

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3. Thank you for providing the list of authors for PubMed listing. Please could you suggest a group name for these authors under which the names will be listed, eg, 'EORTC and CHORUS study investigators'?

I suggest "EORTC and MRC CHORUS study investigators".

**INDIVIDUAL PATIENT DATA META-ANALYSIS OF THE RANDOMISED EORTC  
AND CHORUS TRIALS COMPARING NEOADJUVANT CHEMOTHERAPY  
VERSUS UPFRONT DEBULKING SURGERY IN ADVANCED TUBO-OVARIAN  
CANCERS**

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## SUMMARY

**Background.** Two prospective randomised trials, comparing neoadjuvant chemotherapy (NACT) with upfront debulking surgery (UDS) in advanced tubo-ovarian cancer (EORTC 55971 and MRC CHORUS)-, were analysed with the aim to examine the long term outcomes of the patients and identify any preferable therapeutic approaches for subgroup populations.

**Methods.** Pre-planned individual updated patient data meta-analysis of both trials (NCT00003636 and ISRCTN74802813). , In the EORTC trial eligible women had biopsy proven stage IIIC or IV invasive epithelial tubo-ovarian carcinoma. In the CHORUS, trial the inclusion criteria were similar, but women with apparent stage IIIA and IIIB were also eligible. The main aim of the meta-analysis was to show non-inferiority in overall survival with NACT compared UDS using the “reverse Kaplan-Meier” method. Test for heterogeneity was based on the Cochran’s Q heterogeneity statistic.

**Findings.** 1220 women were randomised. The overall median follow-up was 7.6 years (EORTC 9.2 and CHORUS 5.9 years). Median patient age was 63 years (range 25-88 years) and median size of the largest metastatic tumour at diagnosis was 8 cm (range 0-50 cm). FIGO stage distribution was II-IIIB(4.5%), IIIC(68.1%), IV(18.9%) with 8.5% of data missing. There was no statistically significant difference for the entire population regarding the median overall survival (OS) between patients who underwent UDS and NACT (26.9 and 27.6 months; HR: 0.98, 95% CI: 0.87-1.10; p = 0.688). Median OS for EORTC and CHORUS patients was significantly different at 30.2 and 23.6 months, respectively (HR: 1.20, 95% CI:1.06-1.36;p=0.004) but not significantly heterogeneous (Cochran’s Q p= 0.17). Variable outcomes were noted in some cohorts.

**Interpretation.** Long-term follow-up data confirm that NACT and UDS result in similar OS in advanced tubo-ovarian cancer, with preferential outcomes in some patients. This meta-analysis, with long-term follow-up, confirms that NACT is a valuable treatment option for patients with Stage IIIC-IV tubo-ovarian cancer, especially in patients with a high tumour burden at presentation and/or poor performance status.

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## INTRODUCTION

Over 70% of women with carcinoma of the ovary, fallopian tube or peritoneum (hereafter referred to as tubo-ovarian cancer) present with advanced disease, and usually have a very poor prognosis (1) Since Griffiths reported In 1975 (2) the association between low residual tumour load and improved survival rates following debulking surgery, primary surgery has been embedded in clinical practice as an essential, or even mandatory therapeutic strategy.(3) However, to date, no prospective randomised controlled trials have proven that primary debulking surgery improves the prognosis of patients with advanced tubo-ovarian cancer.

An alternative approach to primary debulking surgery, is neoadjuvant chemotherapy (NACT), administered before attempting cytoreductive surgery. In 2010 the first randomised trial comparing NACT followed by interval debulking surgery (IDS) with upfront debulking surgery (UDS) was published (4). This randomised EORTC (European Organisation for Research and Treatment of Cancer) study showed a similar overall survival (OS) and progression-free survival (PFS) in women with FIGO 1988 (International Federation of Gynecology and Obstetrics) stage IIIC or IV tubo-ovarian cancer with both treatment strategies and a lower operative and postoperative morbidity with NACT. These results were later confirmed in the randomised Medical Research Council (MRC) CHORUS trial (5) and resulted in the acceptance of NACT followed by IDS as an alternative to UDS in stage IIIC and IV tubo-ovarian cancer (6). However, the selection of women with advanced ovarian cancer for NACT or UDS remained controversial (7).

In 2003, while the accrual of the EORTC study was ongoing but prior to the start of the CHORUS trial, we (EORTC/(MRC) planned the current analysis with the aim of analysing the long-term follow-up of both trials and to identify subgroups of women who might benefit more or less from NACT compared with UDS. Herein we report the results of this analysis.

## Methods

93 *Study design and data collection*

94 This is a pre-planned individual updated patient data meta-analysis of the EORTC 55971 and MRC CHORUS  
95 trials. performed according to the PRISMA 2009 guidelines (Figure 1) (84). The eligibility criteria and study  
96 design of the EORTC and CHORUS trials have previously been reported (4,5). In short, in the EORTC trial  
97 eligible women had biopsy proven stage IIIC or IV invasive epithelial ovarian, primary peritoneal, or fallopian  
98 tube carcinoma. If a biopsy was not available, fine needle aspiration showing an adenocarcinoma was  
99 acceptable under the following conditions: presence of a pelvic adnexal mass, and presence of extrapelvic  
100 metastases of  $\geq 2$  cm (measured during diagnostic laparoscopy or laparotomy, and if not done, based on CT  
101 findings) and a CA125 (KU/L)/CEA (ng/mL) ratio  $> 25$ . If any features of the triad were not present then a  
102 biopsy was mandated. If the CA125/CEA ratio was less than 25, investigations to exclude a gastrointestinal  
103 carcinoma were necessary before entry. In the CHORUS, trial the inclusion criteria were similar, but women  
104 with apparent stage IIIA and IIIB were also eligible. In both trials randomisation was to UDS followed by at  
105 least 6 courses of platinum-based chemotherapy, versus 3 courses of NACT (platinum-based) followed by IDS,  
106 and then at least 3 additional courses of platinum based chemotherapy. In women randomised to UDS whose  
107 surgery was completed without optimal cytoreduction, IDS was permitted and these patients were included for  
108 analyses in the UDS arm. Randomisation included stratification with a minimization technique to stratify for  
109 institution, method of biopsy (image-guided, laparoscopy, laparotomy, fine needle aspiration), stage IIIC or IV,  
110 and largest tumour size (excluding ovaries) before surgery (less than 5, 5 – 10, 10.1 - 20 cm, or more than 20  
111 cm). Randomisation used a minimisation method with a random element, which stratified the patients according  
112 to randomising centre, largest radiological tumour size, clinical FIGO 1988 stage, and pre-specified  
113 chemotherapy regimen.

114 *Data analysis*

115 The analysis was designed in 2003 by the chief investigators of the two trials (IV and SK) and members of the  
116 EORTC/MRC trial managing committees. Trial databases were set up to ensure appropriate comparable  
117 information was collected in both trials to allow the planned individual patient data analysis. The women were  
118 followed until data base lock. CHORUS data were transferred to the EORTC Headquarters and analyzed in  
119 cooperation with the authors by the EORTC statistician (CC). The EORTC standard method for deriving median  
120 follow-up time using the “reverse Kaplan-Meier” method calculating time-to-event on all patients was used,  
121 while in the original CHORUS paper the median duration of follow-up of the surviving patients was used.

122 At the planning stage it was estimated that the pooled dataset would contain between 800 and 900 events  
123 (deaths). Assuming a median OS of 3 years, this allowed assessment of non-inferiority (9,10~~8,9~~) with a one-  
124 sided type I error of 0.05 and a power of 80% where inferiority is considered as an increase of more than 18-19%  
125 in hazard. Similarly, it would allow a 90% power in excluding a hazard increase of 22-23%. Applying a two-  
126 sided test of superiority at 5%, the dataset would allow the detection of an 18% increase in hazard with 80%  
127 power.

128 The principal analysis was performed on the intent-to-treat policy and the primary outcome was OS. The  
129 prespecified secondary endpoint was PFS. Prespecified subgroup analyses based on the stratification factors  
130 that were common to both trials (randomising centre, largest tumour size (excluding ovaries) before surgery (less  
131 than 5, 5 – 10, 10.1 - 20 cm, or more than 20 cm), and clinical FIGO 1988 stage) were performed. The  
132 definitions applied for OS and PFS have been previously published (4). Median OS and PFS were estimated by  
133 the Kaplan-Meier method and compared via the log rank test. Hazard ratio estimates and their confidence  
134 intervals were obtained from a Cox proportional hazards model. In those subgroups where the proportional  
135 hazards assumptions was violated, restricted mean survival times were calculated to provide a more useful  
136 general measure to report the average survival times between the two treatment arms (11~~9~~) Multivariable time-  
137 to-event analyses were performed using a Cox proportional hazards model, with univariate screening followed  
138 by a multivariable stepwise selection procedure (12~~4~~). All baseline characteristics and results were checked for  
139 homogeneity between the two studies and stratified per trial where possible. Test for heterogeneity in PFS or OS  
140 was based on the Cochran’s Q heterogeneity statistic The size of the largest metastasis before randomisation was  
141 measured in the EORTC study during diagnostic laparoscopy or laparotomy, and if not done, based on CT  
142 findings. In the CHORUS trial, these measurements were based on CT radiologic imaging only. All analyses  
143 were done using SAS, version 9.4.

144 For details on size of residual tumour, residual tumor per country, type of surgery, number of cycles and type of  
145 chemotherapy, and time to (re)initiation of chemotherapy we refer to the original papers. (4,5).

146 *Role of funding source*

**Comment [A1]:** Reference numbers  
to be changed

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The funders of the studies had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CC, MN and MP had access to MRC CHORUS raw data. CC had access to the EORTC 55971 raw data. The corresponding author (IV) had full access to all the data and had final responsibility to submit for publication. All authors have seen and approved the final version and, after consultation with the collaborators, agreed to submit for publication

## Results

The patient data of both trials were updated and merged into one data-base (data-base lock EORTC June 6<sup>th</sup>, 2015 and CHORUS June 3<sup>rd</sup>, 2014) that contained 1220 randomised patients. Total combined recruitment lasted almost 12 years (EORTC: 670 patients from Oct 12<sup>th</sup>, 1998 to Nov 29<sup>th</sup> 2006; MRC CHORUS: 550 patients from March 5<sup>th</sup>, 2004 to August 26<sup>th</sup>, 2010). Median follow-up was 7.6 years (IQR: 6.0-9.6 years) (EORTC 9.2 years (IQR: 7.3-10.4 years) and CHORUS 5.9 years (IQR: 4.3-7.4 years)). The characteristics of the patients by study and study arm are summarised in Tables 1 and 2, respectively. The pre-treatment characteristics were well balanced between both treatment groups.

Overall survival (OS) and progression-free survival (PFS) for the entire population were similar for NACT and UDS (median respectively for OS 27.6 (IQR: 14.1-51.3) and 26.9 (IQR: 12.7-50.1) months, HR: 0.97, 95% CI: 0.86-1.09; and for PFS respectively 11.6 (IQR: 7.9-17.7) and 11.1 (IQR: 6.4-17.5) (Figure 42). The lower 1-sided confidence of 95% confidence interval for OS and PFS hazard ratios were 0.87 and 0.89, excluding the 18% non-inferiority margin.

OS was significantly better in the EORTC trial compared with the CHORUS trial (median, respectively 30.2 (IQR: 15.7-53.7) and 23.6 (IQR: 10.5-46.9) months; HR: 1.20, 95% CI: 1.06-1.36;  $p = 0.004$ ) (Figure 32), but PFS was similar (median respectively, 11.5 (IQR: 8.0-17.0) and 10.9 (IQR: 6.1-18.1) months; HR 0.96, 95% CI: 0.86-1.08;  $p = 0.0531$ ) (Supplemental file page 1).

OS and PFS according to trial and treatment arms are presented in the Supplemental file (page 2 and 3).

Cochran's Q was not significant for either OS or PFS ( $p = 0.17$  and  $0.32$  respectively).

Median OS was significantly different for Stage IV compared with stage III and stage II (median respectively, 23.3 (IQR: 12.4-40.8), 30.0 (IQR: 15.6-55.7) and 45.4 (IQR: 31.6-NR) months; HR 2.75 and 1.92 for Stage III and IV versus stage II,  $p < 0.001$ ; see Supplemental file page 4). OS was similar for NACT and UDS in stage IIIC patients (median respectively, 30.8 (IQR: 16.5-51.3) and 28.4 (IQR: 14.1-55.7) months; HR: 1.04, 95% CI: 0.90-1.21;  $p = 0.569$ ; Supplemental file page 5). PFS was similar for NACT and UDS in stage IIIC (median respectively, 12.2 (IQR: 8.4-18.3) and 11.7 (IQR: 7.5-19.9) months; HR: 1.06, 95% CI: 0.92-1.22;  $p = 0.429$ ; Supplemental file page 6). However, in patients with stage IV tubo-ovarian cancer NACT resulted in significantly better OS than UDS (Figure 43) (median respectively, 24.3 (IQR: 14.1-47.6) and 21.2 (IQR: 10.0-36.4) months; HR: 0.76, 95% CI: 0.58-1.00,  $p = 0.048$ ). PFS was also significantly better in stage IV disease with NACT than with UDS (median respectively, 10.6 (IQR: 7.9-15.0) and 9.7 (IQR: 5.2-13.2) months; HR: 0.77, 95% CI: 0.59-1.00,  $p = 0.048$ ) (Supplemental file page 7).

OS was best in patients with a largest metastatic extrapelvic tumour size  $< 5$  cm at the time of randomisation (Supplemental file page 8). In patients with stage IIIC disease and a largest metastatic tumour size  $< 5$  cm, the PFS was better with UDS than with NACT (Figure 54A, respectively median 12.2 (IQR: 8.5-23.3) and 11.7 (IQR: 8.3-16.4); HR: 1.36, 95% CI: 1.06-1.75;  $p = 0.017$ ; hazard plots according to largest metastatic tumour size Supplemental file page 9), but the OS was not significantly different (median respectively, 33.0 (IQR: 13.5-78.7) and 30.2 (IQR: 16.5-51.3); HR: 1.26, 95% CI: 0.96-1.65;  $p = 0.092$ , Figure 54B). Due to deviation from the proportional hazards assumption in this subgroup, restricted mean survival times are presented in table 3. Age and performance status were not predictive for treatment effect on survival (Supplemental file, page 10)

## Discussion

This pre-planned analysis of updated data from the EORTC and CHORUS trials on NACT versus UDS in advanced tubo-ovarian cancer (stage IIIC and IV), confirms that with long-term follow-up NACT results in non-inferior OS and PFS compared with UDS. The planned non-inferiority margin, an increase of more than 18-19% in hazard ratio, was well outside the lower confidence bounds (11% and 13% for PFS and OS respectively). Hence, this meta-analysis with long-term follow-up confirmed that both UDS and NACT are 2 possible treatment options for patients with FIGO Stage IIIC or IV tubo-ovarian cancer. However, the analysis also revealed that PFS and OS was significantly better with NACT compared to UDS in patients diagnosed with stage IV disease. On the other hand, women with stage IIIC disease with a largest extrapelvic metastatic tumour



mass of less than 5 cm had a significantly better PFS with UDS. For those with stage III disease and larger sized metastatic disease, either approach resulted in the same OS. In the women with stage IIIC and largest metastatic tumours at diagnosis < 5 cm, both PFS and OS curves have crossing treatment arms indicating deviation from the proportional hazards assumptions. Therefore the restricted mean survival times (table 3) give a better indication of the treatment effect than the median times (Ref 119). These findings indicate that when deciding on a treatment strategy, not only should the risk of perioperative morbidity (6) and the possibility of debulking the patient's disease to zero residual tumour (7) be taken into account, but also FIGO 1988 stage and the extent of the metastatic disease at presentation.

Although in both studies, a cytological diagnosis of malignancy was permitted, with the evolution of our knowledge regarding tubo-ovarian cancer disease subtypes, presently only histology can reliably distinguish between high-grade and low-grade serous carcinomas (132). This is important since low grade serous carcinomas are much less sensitive to chemotherapeutic regimens and primary surgery is an important and much preferred intervention in this group (143). Thus to facilitate optimal decision making, tissue should be obtained for histological diagnosis in all cases and this should be combined with extensive radiological imaging. Obtaining tissue for histological examination is usually possible using image guided biopsy (usually of the omental cake), although a laparoscopic approach is necessary in some cases and provides additional information on disease distribution which can be included in the decision making process. (154-176)

Both trials have been investigating the timing of surgery in advanced tubo-ovarian cancer and have been criticised for their low R0 rates and low survival rates. However, it should be noted that at the time these patients were randomised, NACT was not accepted as an alternative for UDS and the majority of the patients had extensive Stage IIIC or IV disease, visible on CT. Furthermore, in addition to the EORTC 55971 and CHORUS trials, the SCORPION (154) and the JCOG0602 (187) randomised trials concluded that perioperative morbidity was more favourable with interval debulking after neoadjuvant chemotherapy than after primary debulking surgery. Currently, the TRUST trial randomising NACT versus PDS in advanced tubo-ovarian cancer has been developed and is recruiting patients in selected centres with 50% or more R0 rates. The results of this new trial are awaited with interest. A limitation of this meta-analysis might be that in the EORTC trial only patients with stage IIIC and IV were included while in the CHORUS trial also a (limited) number of patients with stage IIIA and B were included. In addition, the number of patients with Stage IIIC-IV disease without residual tumor after UDS tended to be lower in the CHORUS than in the EORTC trial.

Application of the findings of this analysis to the care of every woman with stage IIIC or IV tubo-ovarian cancer should be tempered by the patients' clinical picture. For example, women in these studies had metastatic disease with a high tumour burden at presentation, and many had a poor performance status. (1897) This clinical scenario is not uncommon and improving outcomes for this population is as important (if not more so) than those who have much better prognostic factors. Accepting the caveats implicit within all clinical trials, the results regarding the clinical management of stage IV disease are derived from one of the largest cohorts of women with stage IV disease in phase III studies. Although some stage IV patients have a better prognosis and present with less spread and more easily resectable disease (143) than the majority of Stage IV patients, our data infer that NACT be the standard of care for most patients with stage IV tubo-ovarian cancer, and primary surgery should only be undertaken exceptionally in women selected on an individual basis.

## Declaration of interests

## Contributors

All authors contributed to the design and execution of this study. The draft of the paper has been written by I. V. and S. K. and all authors have been actively involved in the final drafting and approved the manuscript.

**Conflict of interest** M. N. reports grants from MRC CTU / CRUK, during the conduct of the study. N.J. reports that EORTC, the Royal United Hospital (his employing institution) benefited by having support for clinical trials nurse who collected and verified data from some participants in one of the trials reported in this manuscript. C.M. reports personal fees and other (travel expenses) from Roche Farma España, other support (travel expenses) from AstraZeneca and other from Pharmamar outside the submitted work. T.P. reports personal fees and non-financial support from Astra Zeneca, non-financial support from Roche, non-financial support from IGEA Medical, outside the submitted work; and he is co-Chief Investigator for the ICON7 trial of bevacizumab in first line treatment of patients with advanced ovarian cancer. All other authors declare to have no conflicts of interest in relation to this study.

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313	<b>TABLES</b>
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# INDIVIDUAL PATIENT DATA META-ANALYSIS OF THE RANDOMISED EORTC AND CHORUS TRIALS COMPARING NEOADJUVANT CHEMOTHERAPY VERSUS UPFRONT DEBULKING SURGERY IN ADVANCED TUBO-OVARIAN CANCERS

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## SUMMARY

**Background.** Two prospective randomised trials, comparing neoadjuvant chemotherapy (NACT) with upfront debulking surgery (UDS) in advanced tubo-ovarian cancer (EORTC 55971 and MRC CHORUS), were analysed with the aim to examine the long term outcomes of the patients and identify any preferable therapeutic approaches for subgroup populations.

**Methods.** Pre-planned individual updated patient data meta-analysis of both trials (NCT00003636 and ISRCTN74802813). In the EORTC trial eligible women had biopsy proven stage IIIC or IV invasive epithelial tubo-ovarian carcinoma. In the CHORUS, trial the inclusion criteria were similar, but women with apparent stage IIIA and IIIB were also eligible. The main aim of the meta-analysis was to show non-inferiority in overall survival with NACT compared UDS using the “reverse Kaplan-Meier” method. Test for heterogeneity was based on the Cochran’s Q heterogeneity statistic.

**Findings.** 1220 women were randomised. The overall median follow-up was 7.6 years (EORTC 9.2 and CHORUS 5.9 years). Median patient age was 63 years (range 25-88 years) and median size of the largest metastatic tumour at diagnosis was 8 cm (range 0-50 cm). FIGO stage distribution was II-IIIB(4.5%), IIIC(68.1%), IV(18.9%) with 8.5% of data missing. There was no statistically significant difference for the entire population regarding the median overall survival (OS) between patients who underwent UDS and NACT (26.9 and 27.6 months; HR: 0.98, 95% CI: 0.87-1.10; p = 0.688). Median OS for EORTC and CHORUS patients was significantly different at 30.2 and 23.6 months, respectively (HR: 1.20, 95% CI: 1.06-1.36; p=0.004) but not significantly heterogeneous (Cochran’s Q p= 0.17). Variable outcomes were noted in some cohorts.

**Interpretation.** Long-term follow-up data confirm that NACT and UDS result in similar OS in advanced tubo-ovarian cancer, with preferential outcomes in some patients. This meta-analysis, with long-term follow-up, confirms that NACT is a valuable treatment option for patients with Stage IIIC-IV tubo-ovarian cancer, especially in patients with a high tumour burden at presentation and/or poor performance status.

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## INTRODUCTION

Over 70% of women with carcinoma of the ovary, fallopian tube or peritoneum (hereafter referred to as tubo-ovarian cancer) present with advanced disease, and usually have a very poor prognosis (1) Since Griffiths reported In 1975 (2) the association between low residual tumour load and improved survival rates following debulking surgery, primary surgery has been embedded in clinical practice as an essential, or even mandatory therapeutic strategy.(3) However, to date, no prospective randomised controlled trials have proven that primary debulking surgery improves the prognosis of patients with advanced tubo-ovarian cancer.

An alternative approach to primary debulking surgery, is neoadjuvant chemotherapy (NACT), administered before attempting cytoreductive surgery. In 2010 the first randomised trial comparing NACT followed by interval debulking surgery (IDS) with upfront debulking surgery (UDS) was published (4). This randomised EORTC (European Organisation for Research and Treatment of Cancer) study showed a similar overall survival (OS) and progression-free survival (PFS) in women with FIGO 1988 (International Federation of Gynecology and Obstetrics) stage IIIC or IV tubo-ovarian cancer with both treatment strategies and a lower operative and postoperative morbidity with NACT. These results were later confirmed in the randomised Medical Research Council (MRC) CHORUS trial (5) and resulted in the acceptance of NACT followed by IDS as an alternative to UDS in stage IIIC and IV tubo-ovarian cancer (6). However, the selection of women with advanced ovarian cancer for NACT or UDS remained controversial (7).

In 2003, while the accrual of the EORTC study was ongoing but prior to the start of the CHORUS trial, we (EORTC/(MRC) planned the current analysis with the aim of analysing the long-term follow-up of both trials and to identify subgroups of women who might benefit more or less from NACT compared with UDS. Herein we report the results of this analysis.

## Methods

### *Study design and data collection*

This is a pre-planned individual updated patient data meta-analysis of the EORTC 55971 and MRC CHORUS trials, performed according to the PRISMA 2009 guidelines (Figure 1) (8). The eligibility criteria and study design of the EORTC and CHORUS trials have previously been reported (4,5). In short, in the EORTC trial eligible women had biopsy proven stage IIIC or IV invasive epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. If a biopsy was not available, fine needle aspiration showing an adenocarcinoma was acceptable under the following conditions: presence of a pelvic adnexal mass, and presence of extrapelvic metastases of  $\geq 2$  cm (measured during diagnostic laparoscopy or laparotomy, and if not done, based on CT findings) and a CA125 (KU/L)/CEA (ng/mL) ratio  $> 25$ . If any features of the triad were not present then a biopsy was mandated. If the CA125/CEA ratio was less than 25, investigations to exclude a gastrointestinal carcinoma were necessary before entry. In the CHORUS trial the inclusion criteria were similar, but women with apparent stage IIIA and IIIB were also eligible. In both trials randomisation was to UDS followed by at least 6 courses of platinum-based chemotherapy, versus 3 courses of NACT (platinum-based) followed by IDS, and then at least 3 additional courses of platinum based chemotherapy. In women randomised to UDS whose surgery was completed without optimal cytoreduction, IDS was permitted and these patients were included for analyses in the UDS arm. Randomisation included stratification with a minimization technique to stratify for institution, method of biopsy (image-guided, laparoscopy, laparotomy, fine needle aspiration), stage IIIC or IV, and largest tumour size (excluding ovaries) before surgery (less than 5, 5 – 10, 10.1 - 20 cm, or more than 20 cm). Randomisation used a minimisation method with a random element, which stratified the patients according to randomising centre, largest radiological tumour size, clinical FIGO 1988 stage, and pre-specified chemotherapy regimen.

### *Data analysis*

The analysis was designed in 2003 by the chief investigators of the two trials (IV and SK) and members of the EORTC/MRC trial managing committees. Trial databases were set up to ensure appropriate comparable information was collected in both trials to allow the planned individual patient data analysis. The women were followed until data base lock. CHORUS data were transferred to the EORTC Headquarters and analyzed in cooperation with the authors by the EORTC statistician (CC). The EORTC standard method for deriving median follow-up time using the “reverse Kaplan-Meier” method calculating time-to-event on all patients was used, while in the original CHORUS paper the median duration of follow-up of the surviving patients was used.

At the planning stage it was estimated that the pooled dataset would contain between 800 and 900 events (deaths). Assuming a median OS of 3 years, this allowed assessment of non-inferiority (9,10) with a one-sided type I error of 0.05 and a power of 80% where inferiority is considered as an increase of more than 18-19% in hazard. Similarly, it would allow a 90% power in excluding a hazard increase of 22-23%. Applying a two-sided test of superiority at 5%, the dataset would allow the detection of an 18% increase in hazard with 80% power.

The principal analysis was performed on the intent-to-treat policy and the primary outcome was OS. The prespecified secondary endpoint was PFS. Prespecified subgroup analyses based on the stratification factors that were common to both trials (randomising centre, largest tumour size (excluding ovaries) before surgery (less than 5, 5 – 10, 10.1 - 20 cm, or more than 20 cm), and clinical FIGO 1988 stage) were performed. The definitions applied for OS and PFS have been previously published (4). Median OS and PFS were estimated by the Kaplan-Meier method and compared via the log rank test. Hazard ratio estimates and their confidence intervals were obtained from a Cox proportional hazards model. In those subgroups where the proportional hazards assumptions was violated, restricted mean survival times were calculated to provide a more useful general measure to report the average survival times between the two treatment arms (11). Multivariable time-to-event analyses were performed using a Cox proportional hazards model, with univariate screening followed by a multivariable stepwise selection procedure (12). All baseline characteristics and results were checked for homogeneity between the two studies and stratified per trial where possible. Test for heterogeneity in PFS or OS was based on the Cochran’s Q heterogeneity statistic. The size of the largest metastasis before randomisation was measured in the EORTC study during diagnostic laparoscopy or laparotomy, and if not done, based on CT findings. In the CHORUS trial, these measurements were based on CT radiologic imaging only. All analyses were done using SAS, version 9.4.

For details on size of residual tumour, residual tumor per country, type of surgery, number of cycles and type of chemotherapy, and time to (re)initiation of chemotherapy we refer to the original papers. (4,5).

### *Role of funding source*

The funders of the studies had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CC, MN and MP had access to MRC CHORUS raw data. CC had access to the EORTC

55971 raw data. The corresponding author (IV) had full access to all the data and had final responsibility to submit for publication. All authors have seen and approved the final version and, after consultation with the collaborators, agreed to submit for publication

## Results

The patient data of both trials were updated and merged into one data-base (data-base lock EORTC June 6<sup>th</sup>, 2015 and CHORUS June 3<sup>rd</sup>, 2014) that contained 1220 randomised patients. Total combined recruitment lasted almost 12 years (EORTC: 670 patients from Oct 12<sup>th</sup>, 1998 to Nov 29<sup>th</sup> 2006; MRC CHORUS: 550 patients from March 5<sup>th</sup>, 2004 to August 26<sup>th</sup>, 2010). Median follow-up was 7.6 years (IQR: 6.0-9.6 years) (EORTC 9.2 years (IQR: 7.3-10.4 years) and CHORUS 5.9 years (IQR: 4.3-7.4 years)). The characteristics of the patients by study and study arm are summarised in Tables 1 and 2, respectively. The pre-treatment characteristics were well balanced between both treatment groups.

Overall survival (OS) and progression-free survival (PFS) for the entire population were similar for NACT and UDS (median respectively for OS 27.6 (IQR: 14.1-51.3) and 26.9 (IQR: 12.7-50.1) months, HR: 0.97, 95% CI: 0.86-1.09; and for PFS respectively 11.6 (IQR: 7.9-17.7) and 11.1 (IQR: 6.4-17.5) (Figure 2). The lower 1-sided confidence of 95% confidence interval for OS and PFS hazard ratios were 0.87 and 0.89, excluding the 18% non-inferiority margin.

OS was significantly better in the EORTC trial compared with the CHORUS trial (median, respectively 30.2 (IQR: 15.7-53.7) and 23.6 (IQR: 10.5-46.9) months; HR: 1.20, 95% CI: 1.06-1.36;  $p = 0.004$ ) (Figure 3), but PFS was similar (median respectively, 11.5 (IQR: 8.0-17.0) and 10.9 (IQR: 6.1-18.1) months; HR 0.96, 95% CI: 0.86-1.08;  $p = 0.0531$ ) (Supplemental file page 1).

OS and PFS according to trial and treatment arms are presented in the Supplemental file (page 2 and 3).

Cochran's Q was not significant for either OS or PFS ( $p=0.17$  and  $0.32$  respectively).

Median OS was significantly different for Stage IV compared with stage III and stage II (median respectively, 23.3 (IQR: 12.4-40.8), 30.0 (IQR: 15.6-55.7) and 45.4 (IQR: 31.6-NR) months; HR 2.75 and 1.92 for Stage III and IV versus stage II,  $p < 0.001$ ; see Supplemental file page 4). OS was similar for NACT and UDS in stage IIIC patients (median respectively, 30.8 (IQR: 16.5-51.3) and 28.4 (IQR: 14.1-55.7) months; HR: 1.04, 95% CI: 0.90-1.21;  $p = 0.569$ ; Supplemental file page 5). PFS was similar for NACT and UDS in stage IIIC (median respectively, 12.2 (IQR: 8.4-18.3) and 11.7 (IQR: 7.5-19.9) months; HR: 1.06, 95% CI: 0.92-1.22;  $p = 0.429$ ; Supplemental file page 6). However, in patients with stage IV tubo-ovarian cancer NACT resulted in significantly better OS than UDS (Figure 4) (median respectively, 24.3 (IQR: 14.1-47.6) and 21.2 (IQR: 10.0-36.4) months; HR: 0.76, 95% CI: 0.58-1.00,  $p = 0.048$ ). PFS was also significantly better in stage IV disease with NACT than with UDS (median respectively, 10.6 (IQR: 7.9-15.0) and 9.7 (IQR: 5.2-13.2) months; HR: 0.77, 95% CI: 0.59-1.00,  $p = 0.048$ ) (Supplemental file page 7).

OS was best in patients with a largest metastatic extrapelvic tumour size  $< 5$  cm at the time of randomisation (Supplemental file page 8). In patients with stage IIIC disease and a largest metastatic tumour size  $< 5$  cm, the PFS was better with UDS than with NACT (Figure 5A, respectively median 12.2 (IQR: 8.5-23.3) and 11.7 (IQR: 8.3-16.4); HR: 1.36, 95% CI: 1.06-1.75;  $p=0.017$ ; hazard plots according to largest metastatic tumour size Supplemental file page 9), but the OS was not significantly different (median respectively, 33.0 (IQR: 13.5-78.7) and 30.2 (IQR: 16.5-51.3); HR: 1.26, 95% CI: 0.96-1.65;  $p=0.092$ , Figure 5B). Due to deviation from the proportional hazards assumption in this subgroup, restricted mean survival times are presented in table 3. Age and performance status were not predictive for treatment effect on survival (Supplemental file, page 10)

## Discussion

This pre-planned analysis of updated data from the EORTC and CHORUS trials on NACT versus UDS in advanced tubo-ovarian cancer (stage IIIC and IV), confirms that with long-term follow-up NACT results in non-inferior OS and PFS compared with UDS. The planned non-inferiority margin, an increase of more than 18-19% in hazard ratio, was well outside the lower confidence bounds (11% and 13% for PFS and OS respectively). Hence, this meta-analysis with long-term follow-up confirmed that both UDS and NACT are 2 possible treatment options for patients with FIGO Stage IIIC or IV tubo-ovarian cancer. However, the analysis also revealed that PFS and OS was significantly better with NACT compared to UDS in patients diagnosed with stage IV disease. On the other hand, women with stage IIIC disease with a largest extrapelvic metastatic tumour mass of less than 5 cm had a significantly better PFS with UDS. For those with stage III disease and larger sized metastatic disease, either approach resulted in the same OS. In the women with stage IIIC and largest metastatic

tumours at diagnosis < 5 cm, both PFS and OS curves have crossing treatment arms indicating deviation from the proportional hazards assumptions. Therefore the restricted mean survival times (table 3) give a better indication of the treatment effect than the median times (11). These findings indicate that when deciding on a treatment strategy, not only should the risk of perioperative morbidity (6) and the possibility of debulking the patient's disease to zero residual tumour (7) be taken into account, but also FIGO 1988 stage and the extent of the metastatic disease at presentation.

Although in both studies, a cytological diagnosis of malignancy was permitted, with the evolution of our knowledge regarding tubo-ovarian cancer disease subtypes, presently only histology can reliably distinguish between high-grade and low-grade serous carcinomas (13). This is important since low grade serous carcinomas are much less sensitive to chemotherapeutic regimens and primary surgery is an important and much preferred intervention in this group (14). Thus to facilitate optimal decision making, tissue should be obtained for histological diagnosis in all cases and this should be combined with extensive radiological imaging. Obtaining tissue for histological examination is usually possible using image guided biopsy (usually of the omental cake), although a laparoscopic approach is necessary in some cases and provides additional information on disease distribution which can be included in the decision making process. (15-17)

Both trials have been investigating the timing of surgery in advanced tubo-ovarian cancer and have been criticised for their low R0 rates and low survival rates. However, it should be noted that at the time these patients were randomised, NACT was not accepted as an alternative for UDS and the majority of the patients had extensive Stage IIIC or IV disease, visible on CT. Furthermore, in addition to the EORTC 55971 and CHORUS trials, the SCORPION (15) and the JCOG0602 (18) randomised trials concluded that perioperative morbidity was more favourable with interval debulking after neoadjuvant chemotherapy than after primary debulking surgery. Currently, the TRUST trial randomising NACT versus PDS in advanced tubo-ovarian cancer has been developed and is recruiting patients in selected centres with 50% or more R0 rates. The results of this new trial are awaited with interest. A limitation of this meta-analysis might be that in the EORTC trial only patients with stage IIIC and IV were included while in the CHORUS trial also a (limited) number of patients with stage IIIA and B were included. In addition, the number of patients with Stage IIIC-IV disease without residual tumor after UDS tended to be lower in the CHORUS than in the EORTC trial.

Application of the findings of this analysis to the care of every woman with stage IIIC or IV tubo-ovarian cancer should be tempered by the patients' clinical picture. For example, women in these studies had metastatic disease with a high tumour burden at presentation, and many had a poor performance status. (19) This clinical scenario is not uncommon and improving outcomes for this population is as important (if not more so) than those who have much better prognostic factors. Accepting the caveats implicit within all clinical trials, the results regarding the clinical management of stage IV disease are derived from one of the largest cohorts of women with stage IV disease in phase III studies. Although some stage IV patients have a better prognosis and present with less spread and more easily resectable disease (14) than the majority of Stage IV patients, our data infer that NACT be the standard of care for most patients with stage IV tubo-ovarian cancer, and primary surgery should only be undertaken exceptionally in women selected on an individual basis.

## **Declaration of interests**

### **Contributors**

All authors contributed to the design and execution of this study. The draft of the paper has been written by I. V. and S. K. and all authors have been actively involved in the final drafting and approved the manuscript.

**Conflict of interest** M. N. reports grants from MRC CTU / CRUK, during the conduct of the study. N.J. reports that EORTC, the Royal United Hospital (his employing institution) benefited by having support for clinical trials nurse who collected and verified data from some participants in one of the trials reported in this manuscript,. C.M. reports personal fees and other (travel expenses) from Roche Farma España, other support (travel expenses) from AstraZeneca and other from Pharmamar outside the submitted work. T.P. reports personal fees and non-financial support from AstraZeneca, non-financial support from Roche, non-financial support from IGEA Medical, outside the submitted work; and he is co-Chief Investigator for the ICON7 trial of bevacizumab in first line treatment of patients with advanced ovarian cancer. All other authors declare to have no conflicts of interest in relation to this study.



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309

## 310 **LEGEND**

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314 **Table 3.** Restricted mean survival time (RMST) estimates in patients with FIGO stage IIIC and largest  
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319 **Figure 1.** Prisma 2009 Flow Diagram

320 **Figure 2.** Overall survival (Panel A) and progression-free survival (Panel B) according to treatment arm.

321 **Figure 3.** Overall survival according to study.

322 **Figure 4.** Overall survival according to treatment arm in stage IV patients (Panel A Kaplan Meier curves; . Panel  
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325 largest metastatic tumour size < 5 cm at entry (Kaplan Meier curves; Panel A:PFS; Panel B: OS)

Table 1. Baseline characteristics by study

	EORTC (n= 670)	CHORUS (n=550)	TOTAL (n=1220)
Median Age (years) (range)	62 (25-86) IQR: 54.0 - 69.0	65 (26-88) IQR: 58.0 - 72.0	63 IQR: 56.0 - 71.0
Largest metastatic tumor size (mm) (range)	80 (0-400) IQR: 42.0 - 140.0	80 (7-500) IQR: 50.0 - 120.0	80 IQR: 48.0 - 130.0
CA125 at entry (KU/L) (range)	1161 (15-41456) IQR:	1016 (26-39323) IQR:	1089 IQR:

Table 2. Baseline characteristics by allocated treatment

	UDS (n=612)	NACT (n=608)	TOTAL (n=1220)
Median Age (years) (range)	63 (25-87) IQR: 55.0 - 71.0	64 (33-88) IQR: 57.0 - 70.0	63 IQR: 56.0 - 71.0
Largest metastatic tumor size (mm) (range)	80 (0-430) IQR: 49.0 - 130.0	80 (0-500) IQR: 47.0 - 125.0	80 IQR: 48.0 - 130.0
CA125 at entry (KU/L) (range)	1039 (16-39323) IQR: 409.0 - 2547.5	1137 (15-41456) IQR: 446.0 - 2606.0	1089 IQR: 431.0 - 2599.0

1

2

3

**Table 3: restricted mean survival time (RMST) estimates in patients with FIGO Stage IIIC and largest metastatic tumour size < 5 cm at entry**

		RMST	95% CI
Overall survival	UDS	47.3 months	40.4 – 54.1
	NACT	39.3 months	33.9 – 44.8
Progression free survival	UDS	27.5 months	21.2 – 33.8
	NACT	17.0 months	13.8 – 20.2

4

Figure 1

PRISMA 2009 Flow Diagram

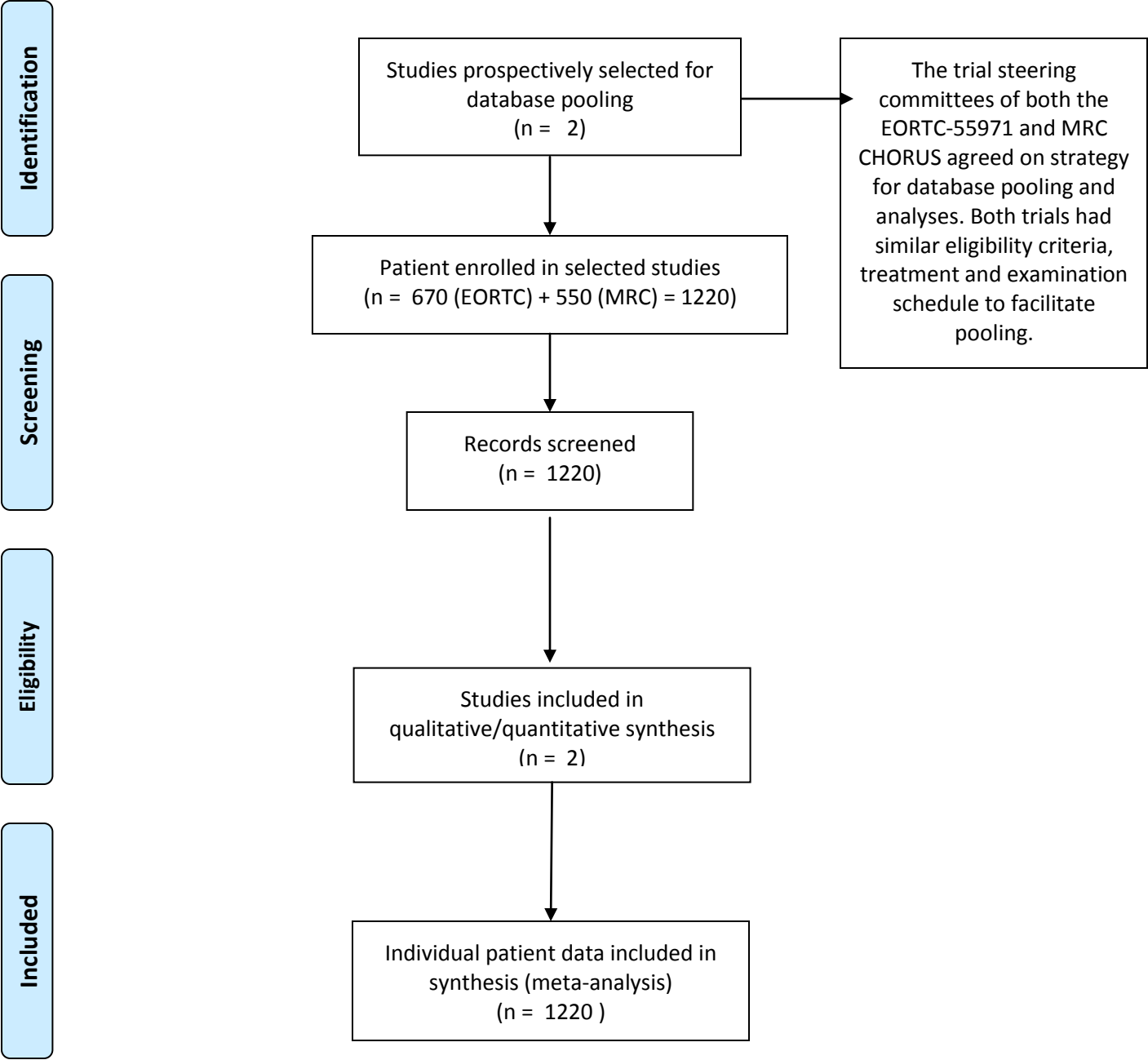
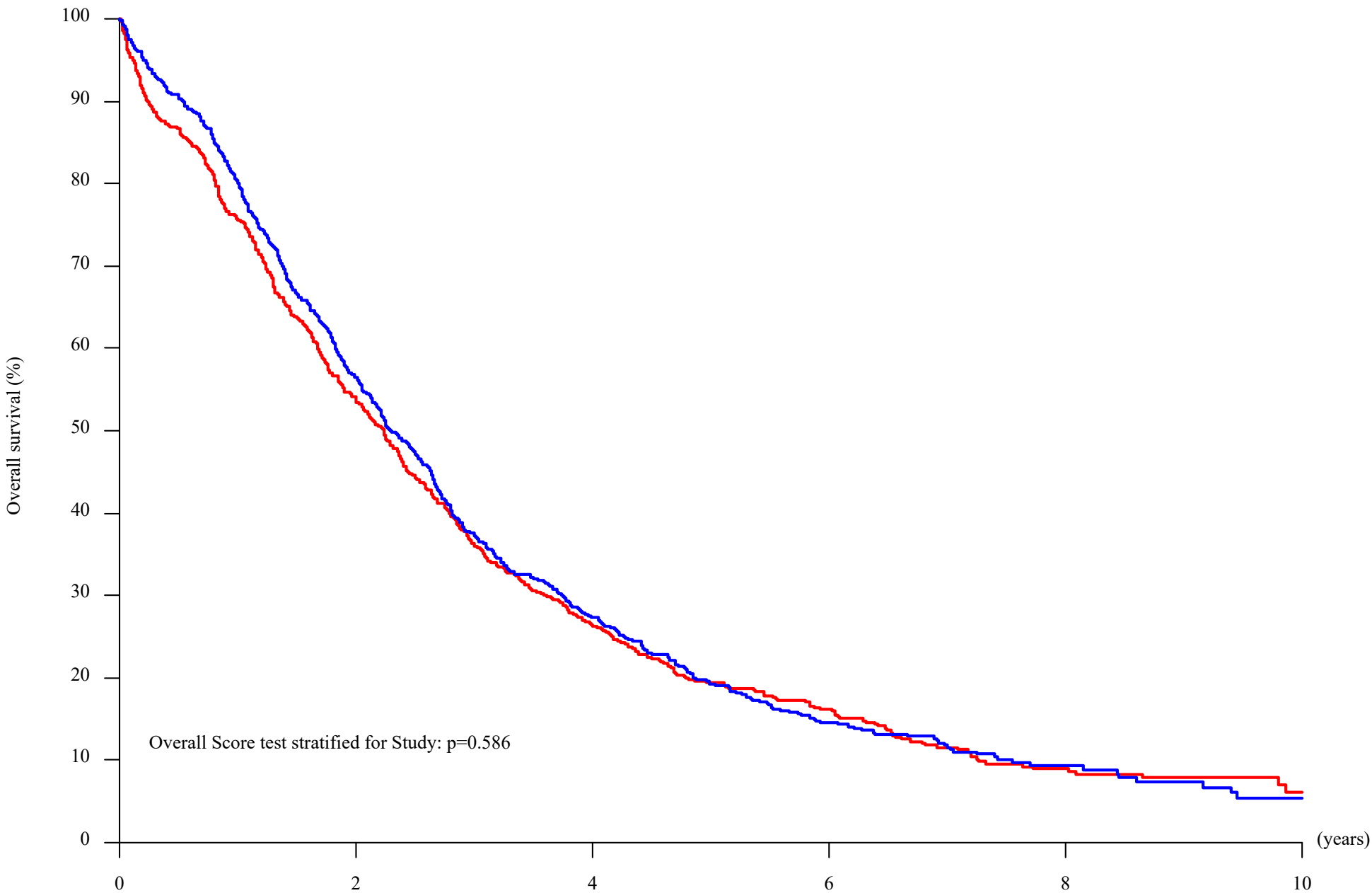


Figure 2 Panel A

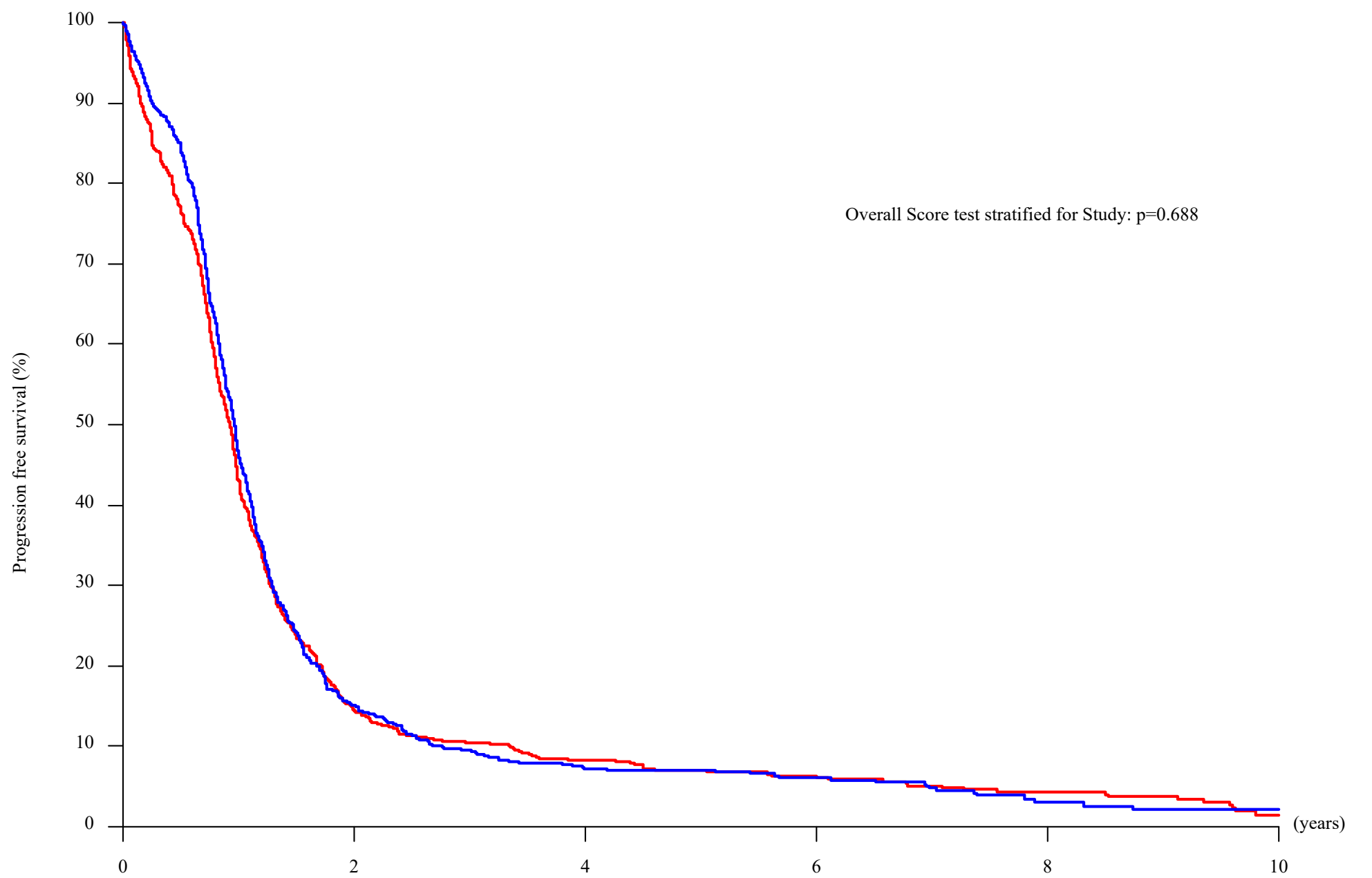
Overall survival



O	N	Number of patients at risk :					Treatment	
528	612	323	149	74	27		<div></div> Upfront debulking surgery	
525	608	338	147	65	22		<div></div> Neoadjuvant chemotherapy	

Figure 2 Panel B

Progression free survival

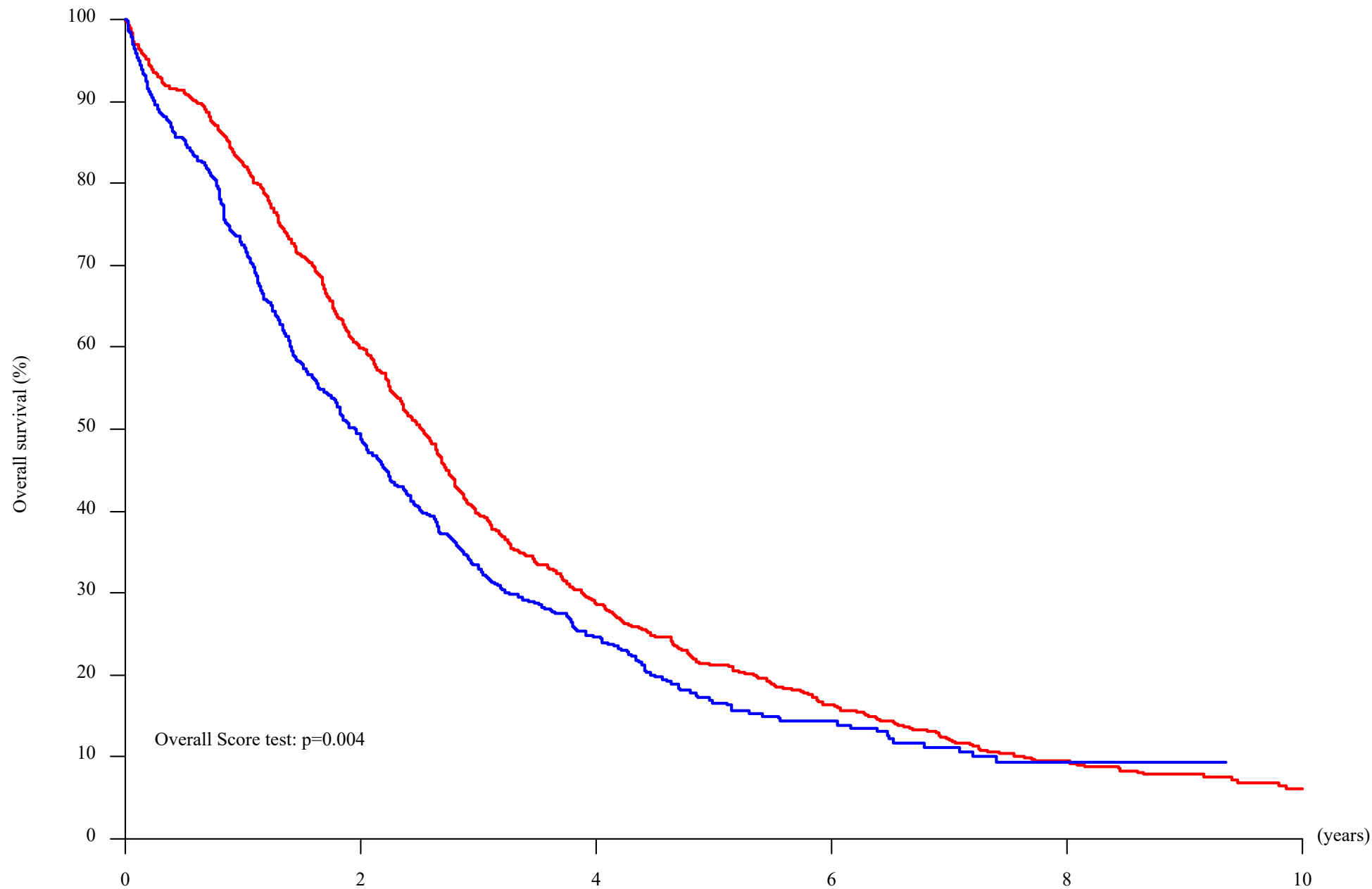


O	N	Number of patients at risk :				Treatment	
		87	48	27	16	<span style="color: red;">—</span>	Upfront debulking surgery
588	612	92	39	26	8	<span style="color: blue;">—</span>	Neoadjuvant chemotherapy



Figure 3

Overall survival

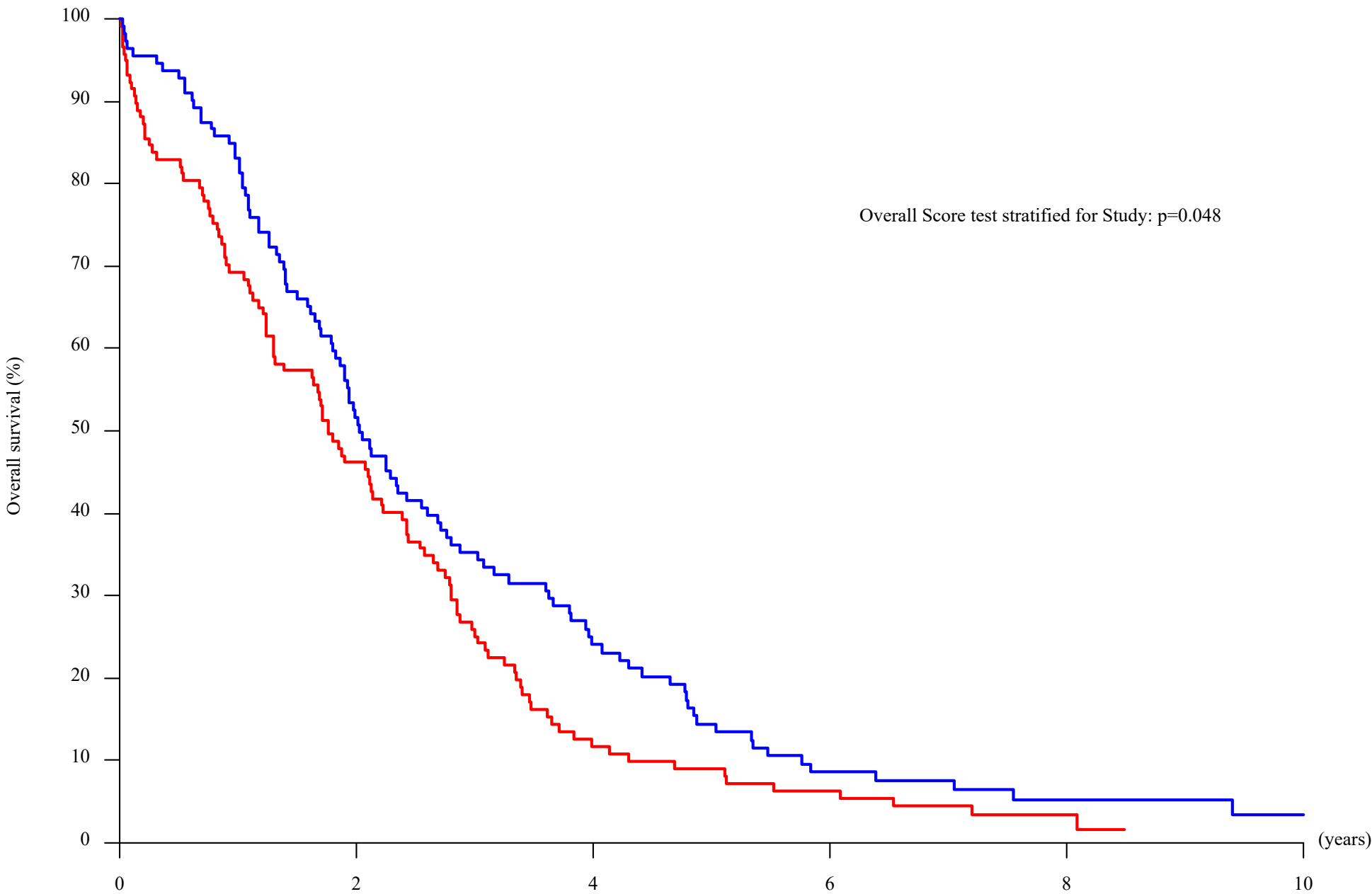


O	N	Number of patients at risk :				Study	
602	670	395	185	102	42	<span style="color: red;">—</span>	EORTC 55971
451	550	266	111	37	7	<span style="color: blue;">—</span>	MRC CHORUS

Figure 4 Panel A

Overall survival

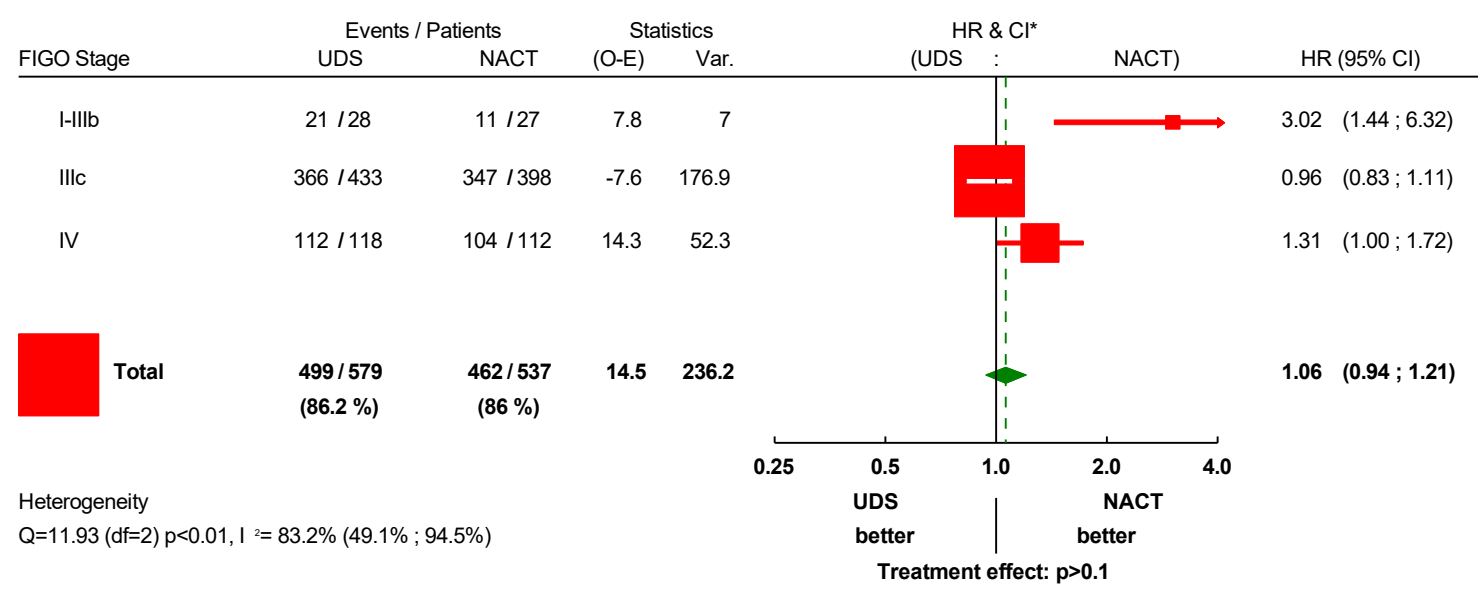
FIGO IV



O	N	Number of patients at risk :				Treatment	
112	118	53	13	7	2	<div></div> Upfront debulking surgery	
104	112	57	25	8	4	<div></div> Neoadjuvant chemotherapy	

Figure 4 Panel B

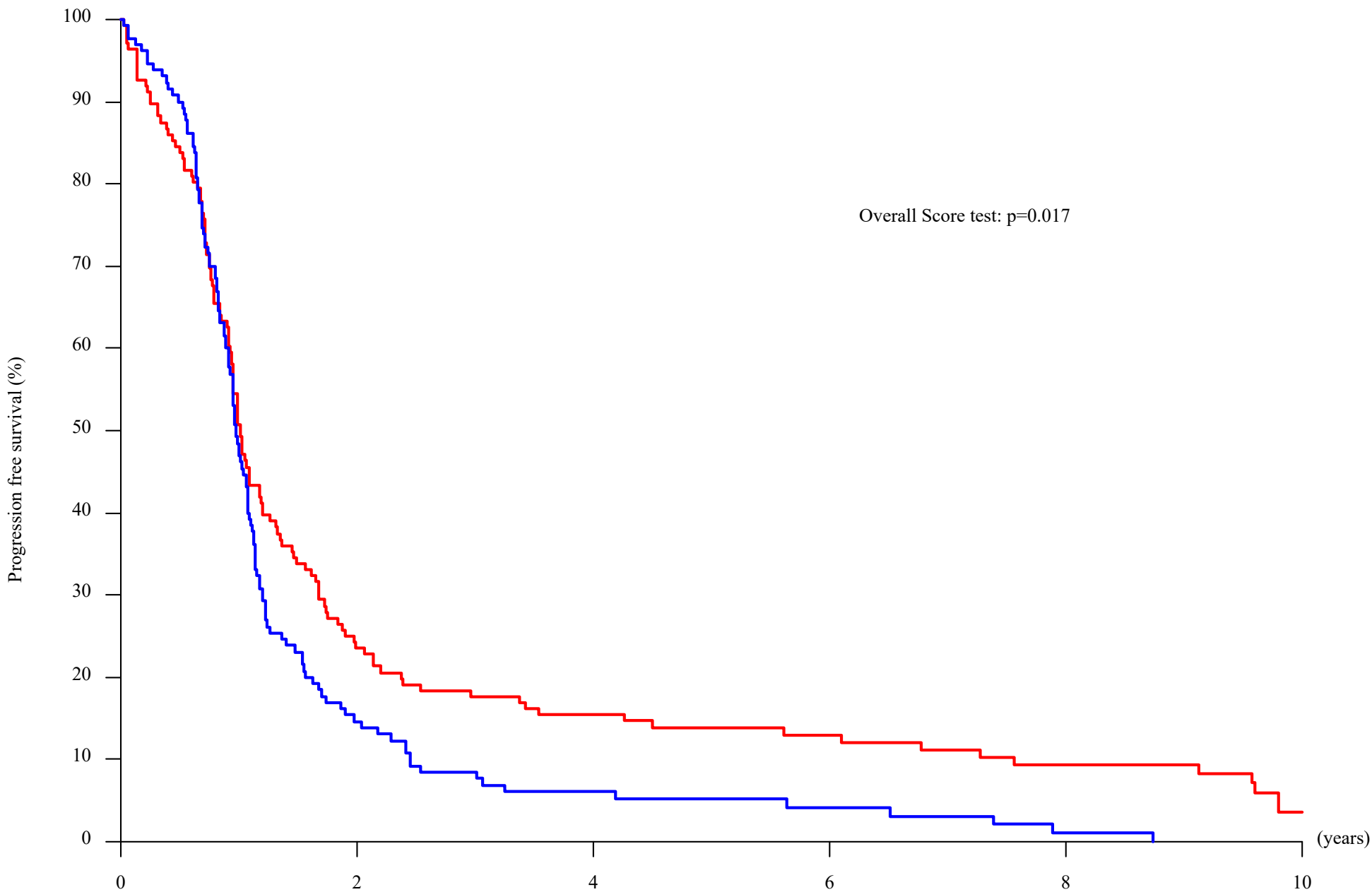
Overall Survival



\*95% CI everywhere

Figure 5 Panel A

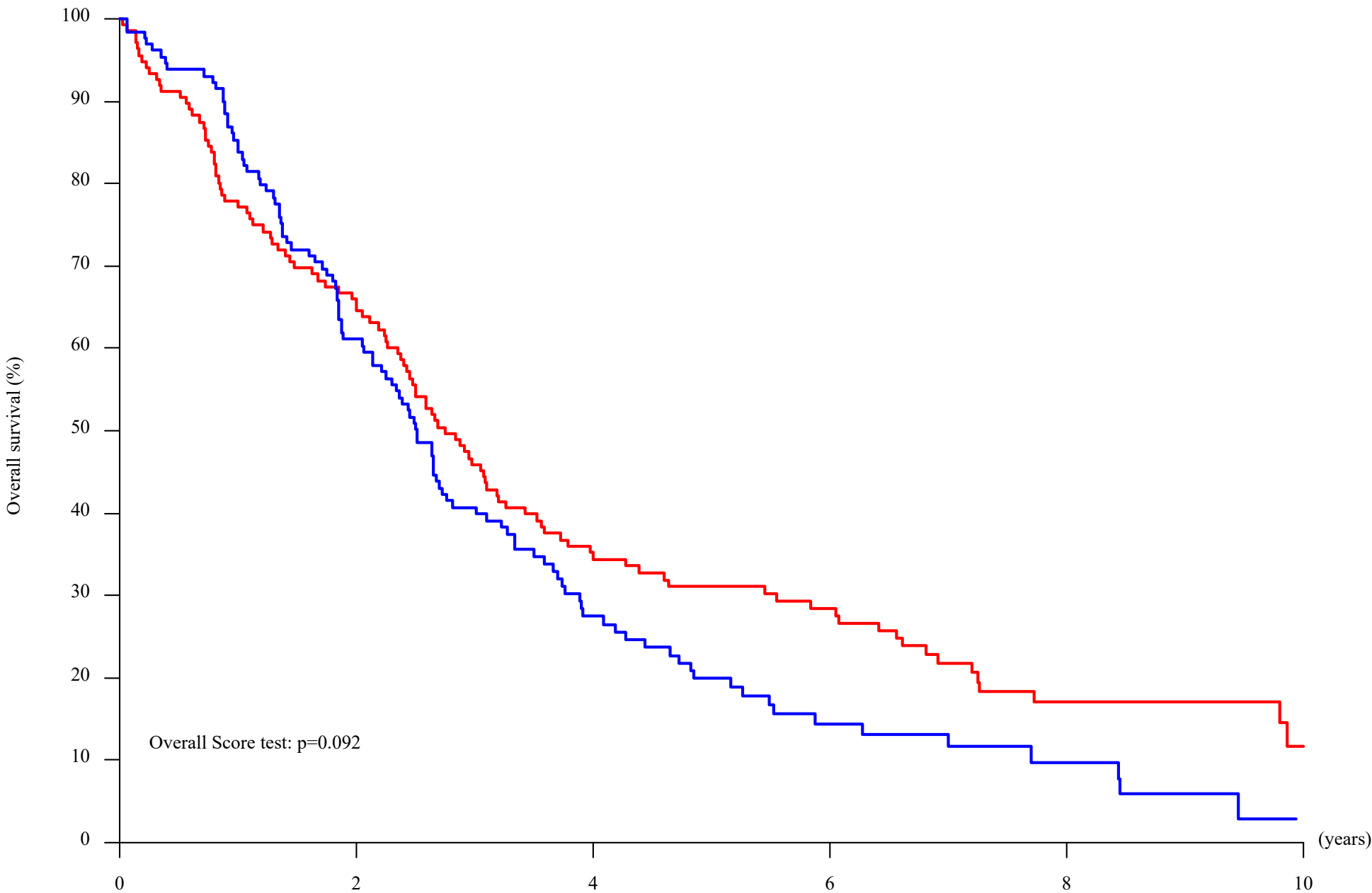
Progression free survival  
FIGO IIIc and <5cm



O	N	Number of patients at risk :				Trtm arm	
130	136	32	21	15	10	UDS	
128	130	19	7	4	1	NACT	

Figure 5 Panel B

Overall survival  
FIGO IIIc and <5cm



O	N	Number of patients at risk :				Trtm arm
108	136	88	44	32	13	UDS
110	130	78	30	12	5	NACT

Supplementary appendix

[Click here to download Necessary Additional Data: Supplemental file Meta-analysis.pdf](#)

Research in context Vergote

[Click here to download Necessary Additional Data: Research in context Vergote resubmission 2 clean.docx](#)

**List of investigators for PubMed**

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Appendix II MRC-EORTC stast plan in data release agreement

[Click here to download Necessary Additional Data: MRC CHORUS\\_EORTC Data disclosure agreement Appendix II.pdf](#)



**CHORUS - A randomised trial to determine the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma**

**Version 2.0**

**5 June 2008**

**EUDRACT number:** 2007-004429-45  
**ISRCTN:** 74802813

**Authorised by:**

**Name:** Prof S Kehoe

**Role:** Chief Investigator

**Signature:** 

**Date:** 5<sup>th</sup> June 2008

**Name:** Dr Ann Marie Swart

**Role:** Senior Clinical Epidemiologist  
MRC CTU

**Signature:** 

**Date:** 5<sup>th</sup> June 2008

**RCOG**



**General Information**

This document describes the CHORUS trial, and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to known investigators in the trial, but centres entering patients for the first time are advised to contact the MRC Clinical Trials Unit (CTU) to confirm they have the most up to date version in their possession. Clinical problems relating to this study should be referred to the Chief Investigator or Medical Oncology Advisor.

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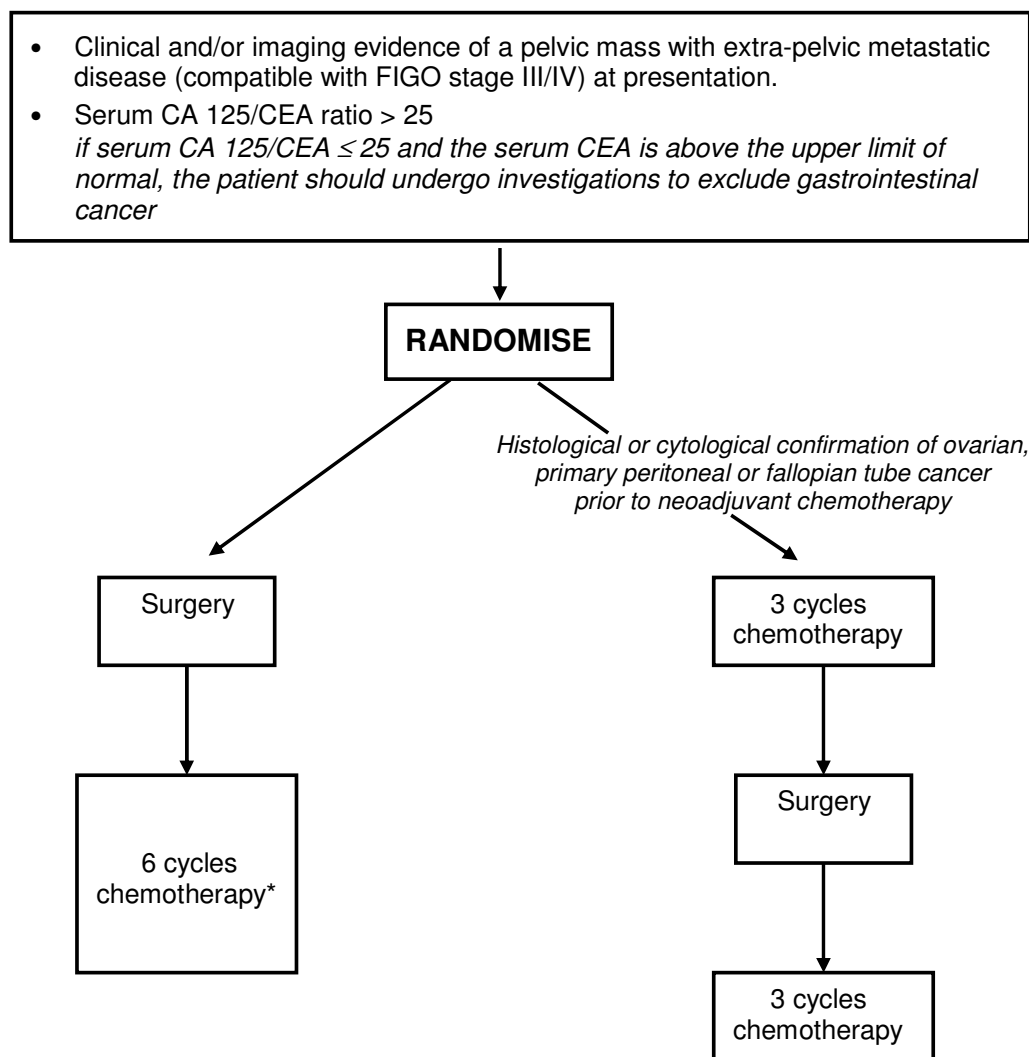
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**ABBREVIATIONS**

<b>AE</b>	Adverse Event
<b>AR</b>	Adverse Reaction
<b>AUC</b>	Area Under the Curve
<b>BSA</b>	Body Surface Area
<b>CEA level</b>	Carcinoembryonic Antigen
<b>CHORUS</b>	Chemotherapy Or Upfront Surgery
<b>CI</b>	Chief Investigator
<b>CRF</b>	Case Report Form
<b>Cr</b>	Serum Creatinine
<b>CTU</b>	Clinical Trials Unit
<b>CrCl</b>	Creatinine Clearance
<b>CT scan</b>	Computed Tomographic Scan
<b>CTA</b>	Clinical Trial Authorisation
<b>CV</b>	Curriculum Vitae
<b>ECOG</b>	Eastern Cooperative Oncology Group
<b>EORTC</b>	European Organisation for Research and Treatment of Cancer
<b>FIGO</b>	International Federation of Gynaecology and Obstetrics
<b>GFR</b>	Glomerular Filtration Rate
<b>HR</b>	Hazard Ratio
<b>ICON</b>	International Collaborative Ovarian Neoplasm
<b>IDMC</b>	Independent Data Monitoring Committee
<b>IDS</b>	Interval Debulking Surgery
<b>IPD</b>	Individual Patient Data
<b>LREC</b>	Local Research Ethics Committee
<b>MRC</b>	Medical Research Council
<b>MHRA</b>	Medicine and Healthcare Regulatory Authority
<b>NCI CTCAE</b>	National Cancer Institute- Common Terminology Criteria for Adverse Events
<b>NCRI</b>	National Cancer Research Institute
<b>ONS</b>	Office of National Statistics
<b>OS</b>	Overall Survival
<b>PFS</b>	Progression Free Survival
<b>QoL</b>	Quality of Life
<b>RCOG</b>	Royal College of Obstetrics and Gynaecology
<b>R&amp;D</b>	Research and Development
<b>SAE</b>	Serious Adverse Event
<b>SAR</b>	Serious Adverse Reaction
<b>SCOTROC</b>	Scottish Randomised Trial in Ovarian Cancer
<b>SCr</b>	Serum Creatinine
<b>SLL</b>	Second Look Laparotomy
<b>SOP</b>	Standard Operation Procedure
<b>SPC</b>	Summary of Product Characteristics
<b>SUSAR</b>	Suspected Unsuspected Serious Adverse Reaction
<b>TAH/BSO</b>	Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy
<b>TMG</b>	Trial Management Group
<b>TSC</b>	Trial Steering Committee
<b>WHO</b>	World Health Organisation
<b>Wt</b>	Weight

## 1. Trial Schema

**Figure 1: CHORUS Trial Schema**



*\*Interval debulking surgery to be carried out midway through planned chemotherapy course **ONLY** if intention stated at randomisation, and if appropriate.*

## 2. Summary

### Type of design

CHORUS is a multi-centre randomised trial designed to evaluate the safety and efficacy of neoadjuvant chemotherapy i.e. chemotherapy given before and after primary surgery compared to standard surgery followed by chemotherapy.

### Patients to be included

CHORUS is a trial predominantly for women with newly diagnosed, suspected advanced ovarian carcinoma. However, women with primary peritoneal or fallopian tube cancer who fulfil other entry criteria, with clinical and/or imaging evidence of extrapelvic metastatic disease at presentation may be randomised.

### Treatment of patients in the Trial

The standard treatment of ovarian cancer is primary cytoreductive surgery followed by 6 cycles of platinum-based chemotherapy. In CHORUS, patients will be randomly assigned to either the standard treatment (primary surgery) arm or to the neoadjuvant chemotherapy arm in which 3 cycles of carboplatin-based chemotherapy will be given followed by radical surgery and a further 3 cycles of carboplatin-based chemotherapy.

Patients randomised to the primary surgery arm will have disease confirmed at surgery. Those who have residual disease following primary surgery and 3 cycles of chemotherapy may have additional interval debulking surgery after the 3<sup>rd</sup> cycle of chemotherapy if their surgeon has specified this prior to randomisation and believes that it is in the best interest of the patient.

Patients randomised to the neoadjuvant chemotherapy arm, who have not had confirmation of cancer prior to randomisation, are required to have histological or cytological confirmation of ovarian, primary peritoneal or fallopian tube cancer prior to starting chemotherapy. This will be performed by laparoscopic assessment (open laparoscopy permitted), image guided trucut biopsy/core biopsy or fine needle aspiration. All women who are fit to have surgery after 3 cycles of chemotherapy are required to undergo cytoreductive surgery. Imaging evidence of no residual disease at mid-treatment assessment is not a reason for not performing radical surgery.

### Duration of treatment

Treatment of patients in both arms includes surgery and 6 cycles (18 weeks) of chemotherapy is expected to be complete after 28 weeks. In the standard treatment (primary surgery) arm, surgery is expected to be performed within 4 weeks after randomisation and chemotherapy to start within 6 weeks after surgery. In the neoadjuvant arm, chemotherapy is expected to start within 4 weeks after randomisation, radical surgery to start as close to 3 weeks after cycle 3 as possible and chemotherapy to restart within 6 weeks following surgery. It should be noted that the duration of treatment may be extended in either arm if treatment delays occur due to toxicity from chemotherapy or delayed recovery from surgery.



**Outcome Measures**

The primary outcome measure is overall survival (OS). The secondary outcome measures include progression-free survival (PFS), safety and patient reported outcomes of quality of life (QoL).

**Evaluation of Outcome Measures**

Patients will be clinically assessed prior to surgery and each cycle of chemotherapy. Regular examinations and blood tests will be performed during treatment to monitor safety. Tumour assessments will be performed after 3 and 6 cycles of chemotherapy and when clinically indicated. After treatment is completed follow-up reports will be requested at 9 months and 12 months after randomisation and every 3 months in the 2nd year, every 6 months in the 3<sup>rd</sup> year after randomisation and then annually. Follow-up forms will record details of disease status, toxicities and any further treatment given.

Patients should be treated for relapse according to standard local practice.

**Sample Size and Data Maturity**

150 patients were randomised in the feasibility study. An additional 400 patients are required to be randomised over a further 48 months. The primary analysis will occur when 550 patients have been randomised and the last patient randomised has been followed for 2 years.

When combined with EORTC 55971 trial, data on a total of 1250 randomised patients will be analysed (550 CHORUS, 704 EORTC 55971) and will reliably exclude a 5-6% difference in 3-year overall survival. This trial is designed as a non-inferiority trial.

### 3. Background and Rationale

Ovarian cancer is the leading cause of death from gynaecological cancer and the fourth most frequent cause of death from cancer in women. In most cases, a combination of surgery and chemotherapy forms the basic management strategy. While there have been improvements in overall survival, mortality rate remains high and there is a significant need to increase the number of treatment options for women with ovarian cancer. The surgical approach in ovarian cancer, of primary surgery followed by chemotherapy, is unique for solid malignant tumours in that primary debulking surgery is advocated for advanced disease, although macroscopic residual disease remains in a significant proportion of patients. Evidence for the standard approach is based on many non-randomised studies, comparing survival of patients with optimum cytoreduction to those suboptimally cytoreduced. The true impact of primary cytoreductive surgery has never been exposed to the accepted standard of a randomised clinical trial. Indeed, a systematic review of non-randomised studies of cytoreductive surgery indicates that platinum-based chemotherapy rather than cytoreductive surgery may be the treatment which primarily influences survival.<sup>1</sup>

Currently only one modestly sized randomised trial provides evidence supporting cytoreductive surgery and this in the context of a second surgical procedure, interval debulking surgery (IDS), specifically in patients with chemosensitive disease.<sup>3</sup> Conversely, the results of another similar sized randomised trial, which investigated the effect of IDS on patients with suboptimally debulked advanced ovarian cancer, suggests that progression-free and overall survival is not altered by IDS.<sup>4</sup> A smaller trial in Birmingham supports this.<sup>5</sup>

Whilst clarification on the role of IDS after primary surgery is required, the most important question to answer is the impact of primary debulking surgery. The main debate surrounding primary debulking surgery in ovarian cancer is the relationship between the ability to achieve successful optimum debulking, inherent tumour biology and chemo-sensitivity. Studies of neoadjuvant chemotherapy may throw some light on this relationship. There are four reports specifically relating to neoadjuvant chemotherapy in ovarian cancer (see Table 1).

Schwartz *et al.*<sup>6</sup> compared 59 women who underwent neoadjuvant chemotherapy, (with debulking surgery after chemotherapy in 41 cases), with 206 women who had primary debulking surgery followed by platinum-based chemotherapy. There was no clear evidence of a survival difference, although the trend favoured conventionally treated patients. However, the neoadjuvant patients had a significantly poorer ECOG score, and some were considered unfit for surgery, whilst in the conventional arm some patients had no macroscopic disease, or were optimally cytoreduced. Thus a poorer survival would have been anticipated in the neoadjuvant patient population. In this trial, diagnosis was made on clinical examination, positive cytology/histology (using trucut biopsy/fine needle aspiration) in conjunction with CT scans.

Surwit *et al.*<sup>7</sup> administered neoadjuvant platinum-based chemotherapy to 29 women with advanced disease diagnosed on clinical/imaging methods with adenocarcinoma confirmed on cytology or trucut biopsy of abdominal tumour. Dose intensive cisplatin or carboplatin was given followed by definitive cytoreductive surgery. The overall median survival was 22.5 months.

Vergote *et al.*<sup>8</sup> reported a retrospective study on a cohort of patients undergoing neoadjuvant chemotherapy, with the use of laparoscopy to facilitate diagnosis followed by IDS. They achieved a crude 3-year survival of 24.8%. The authors concluded that in patients with advanced ovarian carcinoma, and a large tumour load deemed not resectable, neoadjuvant chemotherapy affords an alternative strategy of care.

Jacob *et al.*<sup>9</sup> undertook a prospective non-randomised 3-arm study of advanced ovarian carcinoma using neoadjuvant chemotherapy. In arm 1, 22 patients underwent a diagnostic laparotomy (biopsy only, residual disease >2cm) followed by 2-4 cycles of platinum based therapy, IDS, 6 cycles of platinum therapy and second look laparotomy (SLL). In arm 2, 22 patients with more than 2cm residual disease after primary debulking received 6 cycles of platinum therapy followed by SLL with debulking surgery. In arm 3, 18 patients with more than 2cm residual disease after primary surgery went on to receive immediate re-laparotomy and debulking surgery followed by 6 cycles of therapy and SLL. The median survival in all groups appeared to be similar at 16, 19.3 and 18 months respectively.

**Table 1: Non-randomised Studies of neoadjuvant platinum-based chemotherapy**

Study Reference	No. of patients	Stage	Surgical Procedures	Median Survival
Schwartz <sup>6</sup>	59	IIIc/IV	Debulking (41) after chemotherapy	12.8 months
	206	IIIc/IV	Primary surgery	26.2 months
Surwit <sup>7</sup>	29	IIIc/IV	Debulking after chemotherapy	22.5 months
Vergote <sup>8</sup>	41	III/IV	Interval debulking surgery (IDS)	24.8% at 3yr
Jacob <sup>9</sup>	22	IIIc/IV	Interval debulking surgery and second look laparotomy	16 months
	22	IIIc/IV	Primary surgery and debulking surgery at second look laparotomy	19.3 months
	18	IIIc/IV	Primary surgery, re-laparotomy and debulking surgery at second look laparotomy	18 months

These exploratory studies are small and non-randomised. However, they do raise important questions in managing women with advanced ovarian cancer. Firstly, neoadjuvant chemotherapy does not appear to adversely affect survival compared with conventionally treated patients and secondly, the ability to diagnose disease without resorting to laparotomy is feasible with present diagnostic tools. The optimum approach to debulking in patients with ovarian cancer by either treatment modality requires a prospective randomised trial.

The European Organisation for Research and Treatment of Cancer (EORTC) has performed a similar trial to CHORUS (EORTC 55971) which closed to recruitment in December 2006. First results are not expected until 2008 and since the EORTC trial on its own has only 80% power to exclude a difference of 8%, which is a large difference to accept as 'non-inferiority' in this setting, the results are unlikely to be conclusive. Other trials, considered as positive and influencing clinical practice, like ICON4<sup>10</sup>, showed an absolute difference in 2 year overall survival of 7% between platinum based chemotherapy alone and platinum plus paclitaxel. It is therefore important to conduct CHORUS both to provide additional data on the effect of neoadjuvant chemotherapy and to be able to combine data from EORTC 55971 in a prospective meta-analysis to be able to exclude a 5% difference in overall survival.

Even if neoadjuvant chemotherapy does not itself improve outcome of women with ovarian cancer, robust evidence from these randomised trials of 'non-inferiority' will improve the treatment options with improved flexibility of timing of surgery and chemotherapy and will open up the possibility of new research questions, for example whether surgery can be delayed until all chemotherapy has finished or whether

chemotherapy could replace surgery as primary treatment in women with advanced disease.

This protocol for the full CHORUS trial follows on from the successfully completed CHORUS feasibility study which opened in March 2004. The feasibility study reached its target accrual with good clinical and QoL data return rates and no safety issues were identified.

### *3.1 Additional Considerations*

- The results of an individual patient data (IPD) meta-analysis demonstrated that platinum-based chemotherapy is better than non-platinum therapy in terms of overall survival of patients with ovarian cancer, and that cisplatin and carboplatin are equally effective therapies.<sup>11</sup> However, in view of the superiority of carboplatin with respect to toxicity and quality of life during treatment, carboplatin has been selected as the platinum-based chemotherapy of choice in this trial.<sup>12</sup>
- CHORUS is aimed primarily at women with ovarian cancer, however under certain situations women with primary peritoneal and fallopian tube cancer can be included.
- Extra-ovarian primary peritoneal carcinoma can account for up to 10% of women with a presumed clinical diagnosis of advanced ovarian cancer. The clinical presentation is primarily abdominal distension with ascites, evidence of omental metastasis and raised CA 125. This condition is frequently indistinguishable from advanced ovarian cancer pre-operatively. In addition, there is also little difference between the two groups in terms of epidemiological characteristics, treatment strategy, response to chemotherapy, and prognosis. Because of this, patients with primary peritoneal carcinoma who present with a pelvic mass as well as extra-pelvic disease may be considered for entry to CHORUS.
- Primary cancer of the fallopian tube accounts for only 0.5% of all gynaecologic cancers. As with primary peritoneal cancer, this condition is frequently indistinguishable from advanced ovarian cancer pre-operatively, and the staging and therapeutic management has been adapted to that of ovarian cancer. For this reason, patients with fallopian tube carcinoma, who present with a pelvic mass and extra-pelvic disease may be considered for entry to CHORUS.

## 4. Aims

The aim of this randomised trial is to investigate the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced ovarian, primary peritoneal, or fallopian tube cancer in terms of overall survival, progression-free survival, quality of life, and safety.

## 5. Selection of sites and clinicians

### 5.1 Selection of sites and clinicians

In order for a site to participate in the CHORUS study, the Principal Investigator for the clinical trial site must sign a CHORUS Investigator statement and the nominated person for the Hospital Trust must sign a Clinical Trial Site Agreement (CTSA) based on the "Model agreement for non-commercial research in the NHS".

By signing the investigator statement and the CTSA, the PI and his/her hospital trust agree to the following:

- The clinical trial site regularly undertakes the treatment of ovarian cancer.
- The investigator has appropriate experience of conducting trials according to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and the trial is conducted in compliance with the GCP and applicable regulatory requirements.
- The clinical trial site has an adequate number of qualified staff and adequate facilities, for the foreseen duration of the trial, to conduct the trial properly and safely.
- The clinical trial site has experienced surgeons accredited in gynae-oncology and who specialise in the management of patients with gynaecological malignancies.
- The clinical trial site has appropriate pathologists who specialise in the reporting of gynae-oncology specimens.
- The clinical trial site has trained oncologists to deliver chemotherapy, who specialise in the treatment of ovarian cancer, and who are integrated into the gynae-oncology multi-disciplinary team and are experienced in the care of patients receiving carboplatin and paclitaxel.
- All staff assisting with the trial are to be adequately informed about the protocol and their trial related duties.
- The study must be conducted in accordance with the current protocol and changes will only be made when necessary to protect the safety, rights and welfare of patients.
- Formal protocols are to be in place at the clinical trial site to deal with acute medical or acute surgical complications of treatment.
- The clinical trial site permits monitoring by the MRC Clinical Trials Unit (MRC CTU), and inspection by the appropriate regulatory authorities. This includes direct access to all trial related sites, documents, reports and data.
- The clinical trial site must maintain a trial master file, which will contain essential documents for the conduct of the trial.
- All trial data must be submitted in a timely manner as described in the protocol.
- Individual clinical trial sites may be suspended on the recommendation of the Trial Management Group (TMG) if data returns are poor or if trial conduct is violated in other ways.

- All Serious Adverse Events (SAE) must be reported immediately to the MRC CTU, except for those that the protocol identifies as not requiring immediate reporting.
- Initial SAE reports must be promptly followed by detailed written reports as appropriate.
- No trial data can be disclosed without the approval of the Trial Steering Committee (TSC).
- All trial related documents must be retained for 5 years after the completion of the trial.

### *5.2 Site Approval*

Clinical trial site will be authorised to randomise patients in this trial only when they have returned the following documents to the MRC CTU:

- Confirmation of Local Research Ethics Committee (site-specific assessment) favourable opinion
- Confirmation of Local R&D approval
- Copy of the most recent version of the patient information sheet and consent form on local headed paper
- CV for Principal Investigator
- Clinical Trials Site Agreement
- Signed investigator statement
- Completed delegation log (signature list and delegation of responsibilities)
- Full contact details for all site personnel
- Completed local trial master file self assessment form

For each clinical trial site, the responsibilities and contact details (phone, fax and email address) of each person working on the CHORUS trial must be documented on the Delegation of Responsibility Log. Clinical trial sites must notify MRC CTU of any subsequent changes to trial personnel and/or their responsibilities.

## 6. Selection of patients

### 6.1 Eligibility Criteria

- Imaging evidence (with or without clinical evidence) of a pelvic mass with extra-pelvic metastatic disease (compatible with FIGO stage III/IV) at presentation.  
*Patients must be randomised **within 6 weeks** of the imaging evidence of a pelvic mass.*
- Serum CA 125/CEA ratio  $> 25$  [*if the serum CA 125/CEA  $\leq 25$  and the serum CEA is above the upper limit of normal, the patient should undergo investigations to exclude gastrointestinal cancer*]
- Patient planned to receive **carboplatin-based** chemotherapy
- Patient fit to undergo protocol treatment and follow-up
- No concomitant or previous malignancy likely to interfere with protocol treatments or comparisons. Patients may have received previous adjuvant chemotherapy for other malignancies e.g. breast or colorectal carcinoma if diagnosed over 5 years ago with no evidence of subsequent recurrence.
- Written informed consent of the patient

### 6.2 Screening and pre-randomisation investigation

Assessment of the stage of disease is required prior to randomisation. Clinical staging should include thorough physical examination and imaging of abdominal and pelvic regions, and should be compatible with the FIGO staging criteria (see Appendix E). A chest X ray should also be performed. Histological and cytological disease confirmation prior to randomisation is permitted.

## 7. Randomisation

Before entering any patients into the trial, written informed consent must be obtained from the patient. One copy of the consent form should be given to the patient, one copy should be kept with the hospital notes and one copy should be kept at the local site master file

The baseline Quality of Life questionnaire must also be completed before the patient is informed which treatment has been allocated.

To enter a patient, complete the Randomisation Form, CHORUS/R, and telephone the MRC Clinical Trials Unit on **020 7670 4777** (Monday to Friday, 9 am - 5 pm). The following information must be available after first confirming the patient satisfies the eligibility criteria:

- Protocol title and number
- Name of entering clinician
- Name of entering hospital
- Name of gynaecological surgeon
- Surgery hospital
- Name of oncologist
- Oncology hospital
- Patient's initials
- Date of birth
- Hospital number (at both surgery and oncology hospitals)

- Date of imaging evidence of disease prior to randomisation
- Stage of disease (based on clinical and imaging evidence of disease)
  - *if compatible with stage IV disease, reason why*
- Largest tumour size measured radiologically
- CA 125 level, and date of test
- CEA level, and date of test
- CA 125/CEA ratio
  - *if the CA 125/CEA ratio  $\leq 25$  and the serum CEA is above the upper limit of normal, the patient should undergo investigations to exclude gastrointestinal cancer before randomising*
- WHO performance status (**Appendix D**)
- Chosen carboplatin-based chemotherapy (*single agent carboplatin; carboplatin and paclitaxel; carboplatin and other*)
- Intention to perform interval debulking surgery (*yes or no*)
- Confirmation of the date on which histological or cytological confirmation of disease will be obtained if randomised to neoadjuvant arm.

The patient will be allocated a trial number and treatment arm which should be recorded. Written confirmation of the patient's entry into the trial, the trial number and the treatment allocated will be sent to the hospital by post. Following randomisation, the Randomisation Form (CHORUS/R) should be sent immediately to the MRC Clinical Trial Unit.

**This trial is a comparison of treatment policies; once a patient has been randomised they will remain in the trial and full documentation of cancer treatments and follow up will be required.**



## 8. Pre-treatment Assessments

### 8.1 Disease confirmation (Neoadjuvant Chemotherapy Arm)

Before neoadjuvant chemotherapy, evidence of carcinoma must be established histologically or cytologically (providing the patient has a pelvic mass and CA 125/CEA ratio  $\geq 25$ ).

If randomised to the neoadjuvant chemotherapy arm, patients should undergo one of the following procedures to confirm their malignancy type:

- Laparoscopic assessment (*open laparoscopy permitted*)
- Image guided trucut biopsy/core biopsy
- Fine needle aspiration

Pathological tumour assessments should be performed by a recognised specialist gynaecological pathologist. It is recommended that, in appropriate cases, immunohistochemical markers are used to achieve an accurate diagnosis.

### 8.2 Disease confirmation (Primary Surgery Arm)

Patients randomised to the primary surgery arm should have disease status confirmed by FIGO staging and histology at primary surgery.

## 9. Treatment of Patients

### 9.1 Primary Surgery Arm

Comprises radical surgery followed by 6 cycles of carboplatin-based chemotherapy\* at 3-weekly intervals. The interval between randomisation and the initiation of surgery should be a maximum of 4 weeks. Chemotherapy should commence within 6 weeks of primary surgery.

*Interval debulking surgery may be carried out at the discretion of the clinician if appropriate and if stated as the intention prior to randomisation; this should be carried out as close as possible to 3 weeks after the 3<sup>rd</sup> cycle of chemotherapy. Chemotherapy should be resumed within 6 weeks of interval debulking surgery.*

### 9.2 Neoadjuvant Chemotherapy Arm

Comprises histological or cytological confirmation of disease followed by 3 cycles of carboplatin-based chemotherapy\* at 3-weekly intervals. Neoadjuvant chemotherapy should be started within 4 weeks of randomisation. Surgery following neoadjuvant chemotherapy to be performed as close as possible to 3 weeks after the 3<sup>rd</sup> cycle of chemotherapy. A further 3 cycles of carboplatin-based chemotherapy\* should be given within 6 weeks of surgery.

\*The treatment schedule in CHORUS is compatible with SCOTROC4 trial (See section 10.3 for more details)

## 10. Treatment Details

### 10.1 Chemotherapy

Six, 3-weekly cycles of carboplatin, as a single agent or in combination with a taxane or other chemotherapy are to be given according to standard local practice. Experience in the use of these drugs is essential. Dose reduction may be required and recommended dose modifications are provided in **Appendix B**.

The choice of chemotherapy regimen may be made on an individual patient basis, but **must** be specified prior to randomisation. Patients randomised to primary surgery arm will have surgery prior to any chemotherapy. Those allocated to neoadjuvant chemotherapy arm will have surgery after the 3<sup>rd</sup> cycle of chemotherapy.

#### Carboplatin

##### Minimum recommended dose

*Carboplatin*                      5 x (<sup>51</sup>Cr-EDTA clearance + 25) mg  
or  
6 x (calculated or 24hr urinary clearance +25) mg  
repeated every 3 weeks for 6 cycles

##### **Renal function**

GFR should be measured before the first cycle, by <sup>51</sup>Cr-EDTA clearance if possible. Subsequent doses of carboplatin should usually be based on this value of GFR. However, if the patient's serum creatinine changes significantly (>10% change from baseline value), the GFR must be re-measured/re-calculated in order to determine the correct dose of carboplatin to maintain the appropriate AUC. The reason for any change in GFR should also be considered. Urinary tract infection, and the development of ureteric obstruction, should be excluded by the appropriate investigations.

[See **Appendix A** for more information on measurement/calculation of GFR.]

#### Carboplatin and Paclitaxel

##### Minimum recommended dose

*Carboplatin*                      5 x (<sup>51</sup>Cr-EDTA clearance + 25) mg  
or  
6 x (calculated or 24 hr urinary clearance +25) mg

*Paclitaxel*                        175mg/m<sup>2</sup>

repeated every 3 weeks for 6 cycles

Appropriate anti-emetic and hypersensitivity prophylaxis should be administered as per local guidelines.

[See **Appendix A** for more information on measurement/calculation of GFR.]

### 10.2 Surgery

Radical surgical procedures in both arms should be performed by a surgeon with specialist expertise in gynaecological oncological surgery. Surgeons wishing to participate in CHORUS should satisfy one of the following eligibility criteria:

- Consultant gynaecologists with specialist expertise in gynaecological oncology who perform the majority of gynaecological cancer workload in their unit.
- Consultant gynaecological oncologists who have obtained recognition of their subspecialty training or experience by the RCOG.

The name of the surgeon performing the procedure will be required at randomisation.

**The recommended procedures for radical surgery will be as follows:**

- Midline incision
- Sampling of free fluid or peritoneal washings for cytology
- Thorough examination of the peritoneal cavity, liver, gall bladder, diaphragm, large and small bowel, stomach, peritoneal surfaces, pelvis, omentum, and retroperitoneal spaces
- Hysterectomy, bilateral oophorectomy and omentectomy
- Tumour debulking with the intention of leaving **no macroscopic disease**
- Documentation of residual tumour size and location

Whilst the intent of radical surgery should always be clearance of all macroscopic disease, in cases where this is obviously not feasible the disease should be correctly staged, tumour samples collected and any other surgical procedure deemed necessary on clinical grounds performed. Biopsy of pelvic and para-aortic nodes should be performed in patients who appear to have FIGO stage IIIb disease or less.

Facilities and expertise for bowel resection or diversion and para-aortic/pelvic lymphadenectomy should be immediately available. The decision as to whether these procedures are justifiable will depend on the surgeons overall assessment of each patient, but the necessary expertise/facilities **must** be available. It is recognised that achieving cytoreduction may require procedures such as resection of large or small bowel, stoma formation, splenectomy, partial cystectomy and para-aortic/pelvic lymphadenectomy. These procedures should only be undertaken if they will facilitate cytoreduction to less than 1cm residual tumour deposits.

Patients in the **primary surgery arm** for whom the intention was to perform IDS (as stated at randomisation) should not have this procedure if:

- They are shown to have progressive disease
- They had optimal debulking primary surgery (including TAH/BSO, omentectomy) leaving <1cm residual disease
- There is no evidence clinically/radiologically of disease requiring excision.

### 10.3 Co-enrolment

Double randomisation in the SCOTROC4 (A Prospective, Multicentre, Randomised Trial of Carboplatin Flat Dosing Vs Inpatient Dose Escalation in First Line Chemotherapy of Ovarian, Fallopian Tube and Primary Peritoneal Cancers) is allowed, as is MRC OV07/EORTC 55041 (Erlotinib in Ovarian Cancer).

## 11. Schedule of Assessment and Follow-up

All assessments and trial procedures must be performed in compliance to the most up to date version of the protocol, ICH-GCP, any relevant research governance and other regulatory requirements as appropriate.

Summary information on timing of interventions and assessments for safety and efficacy are given in Table 2.

### 11.1 Case Report Form Schedule

- **Randomisation Form (CHORUS/R)** to be completed prior to randomisation.
- **Disease Confirmation Form (CHORUS/DC)** to be completed for patients allocated to neoadjuvant chemotherapy, following histological or cytological confirmation of disease (prior to first cycle of chemotherapy). A copy of the pathology report should be sent to the MRC Clinical Trials Unit for reference.
- **Chemotherapy Form (CHORUS/C)** to be completed after each cycle of chemotherapy.
- **Disease Assessment Form (CHORUS/DA)** to be completed after 3 cycles of chemotherapy has been received, and at termination of protocol treatment, or if protocol treatment discontinued prematurely. (see section 11.3 for further details)
- **Surgery Form (CHORUS/S)** to be completed by the surgeon after primary surgery, or surgery following neoadjuvant chemotherapy. If surgery was not performed, this form should still be completed at approximate time of planned surgery.
- **Interval Debulking Surgery Form (CHORUS/IDS)** to be completed for patients allocated to primary surgery by the surgeon **after** interval debulking surgery (if intention stated at randomisation). If interval debulking surgery was not performed, this form should still be completed at approximate time of planned surgery.
- **Follow-up Form (CHORUS/FU)** at 9 months after randomisation and then every 3 months for the first 2 years, every 6 months for the following 3 years, and then annually.
- **Follow-up Form for Ineligible Patients (CHORUS/FUIP)** to be completed every 6 months for the first 2 years and then annually for patients confirmed with either no disease or a malignancy type that render them ineligible after randomisation. QoL Questionnaires are not required for this group of patients.
- **Progression Form (CHORUS/PD)** to be completed at time of first progression. If first progression is based on an elevated CA 125 level only, a second form should be completed at time of first clinical/radiological progression.
- **Quality of Life Questionnaire** to be completed prior to randomisation, after the 3<sup>rd</sup> and 6<sup>th</sup> cycle of chemotherapy, and at 6 and 12 months after randomisation.

### 11.2 Clinical follow up

After treatment is completed follow-up reports will be requested at **9 months after randomisation, then every 3 months for the first 2 years, every 6 months for 3 years thereafter and then annually**. These follow-up reports will record details of disease status, toxicities and any further treatment given. Patients should be treated for relapse according to local practice. **Once randomised, all patients remain in the trial,**

**and clinical forms are required even when a patient does not receive protocol treatment.**

#### *11.2.1 Long term follow-up*

Every effort should be made to follow-up patients who have been randomised. Patients should, if possible, remain under the care of an oncologist or gynaecologist for the duration of the trial. If the care of a patient is returned to the General Practitioner, it is still the responsibility of the investigator to ensure that the follow-up data required by the protocol is collected and reported. The consent of patients should be obtained for their names to be flagged for survival information through national registries.

#### *11.3 Disease Assessment*

Disease status should be assessed by clinical examination and imaging of abdomen and pelvis prior to randomisation for all patients. For those in the standard treatment arm it is also assessed midway through treatment (after 3 cycles of chemotherapy), and at end of treatment (after 6 cycles, or if protocol treatment stopped prematurely for whatever reason). For patients in the neoadjuvant arm, mid-treatment disease assessment should be carried out after the 3<sup>rd</sup> cycle of chemotherapy, **prior to any surgery**. CT scanning is the preferred cross-sectional imaging modality; however, MRI is considered an acceptable technique.

Measurement of disease progression should be based on the criteria outlined in **Appendix C**.

#### *11.4 Trial Closure*

The trial will be considered closed after data on overall survival (primary outcome) are sufficiently mature (as defined in the protocol) for the primary publication. Further observational follow-up of all patients enrolled in the trial may continue indefinitely. This will initially be via hospital and clinics, but in the longer term may exploit national registers.

Table 2: Trial Assessment Schedule

	Screening	Random- isation	Treatment Period							Follow up
			Cycle 1	Cycle 2	Cycle 3	Midway	Cycle 4	Cycle 5	Cycle 6	End
Informed consent	✓									
Medical history	✓									
Physical examination	✓					✓				✓
Height			✓							
Weight			✓	✓	✓		✓	✓	✓	
Performance Status	✓		✓	✓	✓		✓	✓	✓	✓
CA125	✓		✓	✓	✓		✓	✓	✓	✓ <sup>8</sup>
CEA	✓									
Investigation to exclude GI cancer <sup>1</sup>	✓									
Disease Confirmation (Histology or cytology)		✓ <sup>2</sup>								
Carboplatin based chemotherapy			✓	✓	✓		✓ <sup>6</sup>	✓	✓	
Primary Surgery		✓ <sup>3</sup>				✓ <sup>4</sup>				
Interval Debulking Sugery						✓ <sup>5</sup>				
Tumour assessments	✓					✓				✓ <sup>8</sup>
Chest X-ray	✓									
QoL Forms	✓					✓				✓
Tumour Tissue Block		✓				✓				
Adverse Event		✓ <sup>7</sup>	✓	✓	✓	✓ <sup>7</sup>	✓	✓	✓	✓

1. If serum CA125/CEA  $\leq 25$  and the serum CEA is above the upper limit of normal
2. For women randomised to the neoadjuvant arm, disease confirmation performed prior to randomization is also permitted.
3. For women randomised to the primary surgery arm, surgery should be performed within 4 weeks of randomisation
4. For women randomised to the neoadjuvant arm, surgery should be performed as close to 3 weeks after the 3<sup>rd</sup> cycle of chemotherapy
5. For women randomised to the primary surgery arm, interval debulking surgery should be performed as close to 3 weeks after the 3<sup>rd</sup> cycle of chemotherapy
6. Chemotherapy should be resumed within 6 weeks of either interval debulking surgery (primary surgery arm) or primary surgery (neoadjuvant arm)
7. Adverse event collected at primary surgery or interval debulking surgery
8. After completion of protocol treatment, 1<sup>st</sup> progression can be based on either serum CA125 or tumour assessment (CT or MRI of the pelvis and abdomen). Detailed guidance is outlined in Appendix C

## **12. Discontinuation of trial intervention and withdrawal of consent**

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection.

### *12.1 Discontinuation from trial intervention*

A patient may discontinue trial treatment for the following reasons:

- Progression whilst on therapy
- Unacceptable toxicity
- Patient refusal of trial treatment
- Any alterations in the patient's condition or any intercurrent illness which justifies the discontinuation of treatment in the investigator's opinion.

If a patient wishes to discontinue trial treatment, centres should nevertheless explain clearly to patient the importance of remaining on trial follow-up. This is because the data analysis is set up based on intention to treat, all the follow-up information (including quality of life and progression data) collected will be included in the data analysis.

### *12.2 Withdrawal of Consent*

In rare circumstances, patients may withdraw their consent to participate in the trial. If the patient explicitly states their wish not to contribute further data to the trial, MRC CTU should be informed in writing and the withdrawal of consent should be documented by the investigator in the patient's case report form.



### 13. Serious Adverse Events (SAEs)

This trial is aimed at assessing the impact of timing of surgery and chemotherapy in patients with advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer. The effects and toxicities of individual chemotherapy regimens are not being formally considered, however ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions to IMP in clinical trials.

In addition all serious adverse events that are considered by the responsible clinician to be related to the surgical procedures outlined in this protocol should also be notified to the MRC CTU, these events will be reviewed by the IDMC. Any SAE that is related (to chemotherapy and surgery) and unexpected will be reported to the Main research ethics committee (REC).

#### 13.1 Definitions of Adverse Events/Reactions

The definitions from ICH GCP apply in this trial protocol. These definitions are given in Table 3

**Table 3: Definitions of Adverse Events/Reactions**

Term	Definition
<b>Adverse Event (AE)</b>	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
<b>Adverse Reaction (AR)</b>	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
<b>Serious AE (SAE) or Serious AR (SAR)</b>	Any untoward medical occurrence or effect that at any dose: <ul style="list-style-type: none"> <li>▪ results in death</li> <li>▪ is life-threatening<sup>1</sup></li> <li>▪ requires hospitalisation or prolongation of existing hospitalisation<sup>2</sup></li> <li>▪ results in persistent or significant disability or incapacity</li> <li>▪ consists of a congenital anomaly or birth defect</li> </ul>
<b>Suspected Unexpected Serious Adverse Reaction (SUSAR)</b>	A SUSAR is a SAR that is classified as 'unexpected' i.e. a serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to

<sup>1</sup> The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

<sup>2</sup> Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

prevent one of the other outcomes listed in the definition above, should also be considered serious. Other non-serious AE/AR should be reported on the side effects of treatment section of chemotherapy form (CHORUS/C) or the surgical complications section of the surgery (CHORUS/S) or interval debulking surgery form (CHORUS/IDS).

### *13.2 CHORUS Specific Exceptions to Seriousness Criteria*

The following events, in the context of this trial, should not be considered as SAEs. No SAE form is required and they are exempt from expedited reporting.

- Disease progression or death as a result of disease progression
- Elective hospitalisation and any non protocol-surgery for treatment of ovarian cancer, primary peritoneal cancer, fallopian tube cancer or its complications.
- Elective hospitalisation to simplify treatment or procedures.
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment.

### *13.3 Clinical Trial Site/Investigator Responsibilities*

All non-serious AEs/ARs, whether expected or not, should be recorded in the toxicity (symptoms) section of the appropriate CRF. The relevant subset of the NCI Common Terminology Criteria for Adverse Event v3.0 (<http://ctep.cancer.gov/reporting/index.html>) should be used for reporting and grading the severity (i.e. intensity) of operative injuries encountered during radical surgery, and all toxicities experienced during chemotherapy given in this trial, and at follow-up.

SAEs/SARs should be notified to the MRC CTU as described below.

A flowchart (Figure 2) is given at the end of this section to help explain the notification procedures. Any questions concerning this process should be directed to the MRC CTU.

### *13.4 Investigator Assessment*

#### 13.4.1 SERIOUSNESS

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is **serious** using the definitions given in Table 3. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and faxed to MRC CTU.

#### 13.4.2 CAUSALITY

The Investigator must assess the causality of all adverse events in relation to the chemotherapy and surgery using the definitions in Table 3. There are 5 causality categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related then for reporting purposes the event will not be regarded as an adverse reaction to trial therapy. If the causality is assessed as either possible, probable or definitely related then for reporting purposes the event is classified as an adverse reaction. (see Table 4).

#### 13.4.3 EXPECTEDNESS

The investigator must assess the expectedness of all serious adverse reactions in relation to chemotherapy only from the list of expected toxicities provided in **Appendix F**. The expected toxicities are based on the information of the current SPCs for carboplatin and paclitaxel. Investigators must file the current version of the Expected Adverse

Events listing in the safety reporting section of their Investigator File, and use this list to determine the expectedness of all serious adverse reactions. If other chemotherapy drugs are used in CHORUS then the investigator must assess expectedness against the current SPC for the specific drugs used.

Medically qualified staff at the MRC CTU and/or the Chief Investigator (or a medically qualified delegate) will assess the expectedness of all serious adverse reactions reported in relation to surgery (based on the surgical complications criteria on the surgery form).

**Table 4: Definitions of Causality**

<b>Relationship</b>	<b>Description</b>	<b>Event Type</b>
<b>Unrelated</b>	There is no evidence of any causal relationship	Adverse event
<b>Unlikely</b>	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication/surgery). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Adverse event
<b>Possible</b>	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication/surgery). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	Adverse reaction
<b>Probable</b>	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Adverse reaction
<b>Definitely</b>	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Adverse reaction

### 13.5 Notification

#### 13.5.1 NOTIFICATION PROCEDURE:

1. The SAE form must be completed by the investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.
2. Initial SAE reports must be faxed to the contacts shown in Table 5 within one working day of the investigators' knowledge of the event.
3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if

necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' and faxing to the MRC CTU as soon as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

4. Staff at the clinical trial site must **notify** their local research ethics committee (LREC) of the event (as per the clinical trial sites standard local procedure).

**Table 5: SAE Notification Procedure**

Country/Group	Procedure
UK (MRC/NCRI)	Notify MRC CTU by FAX: <b>020 7670 4818</b>
All other groups	Notify MRC CTU by FAX: <b>+44 (0) 20 7670 4818</b>

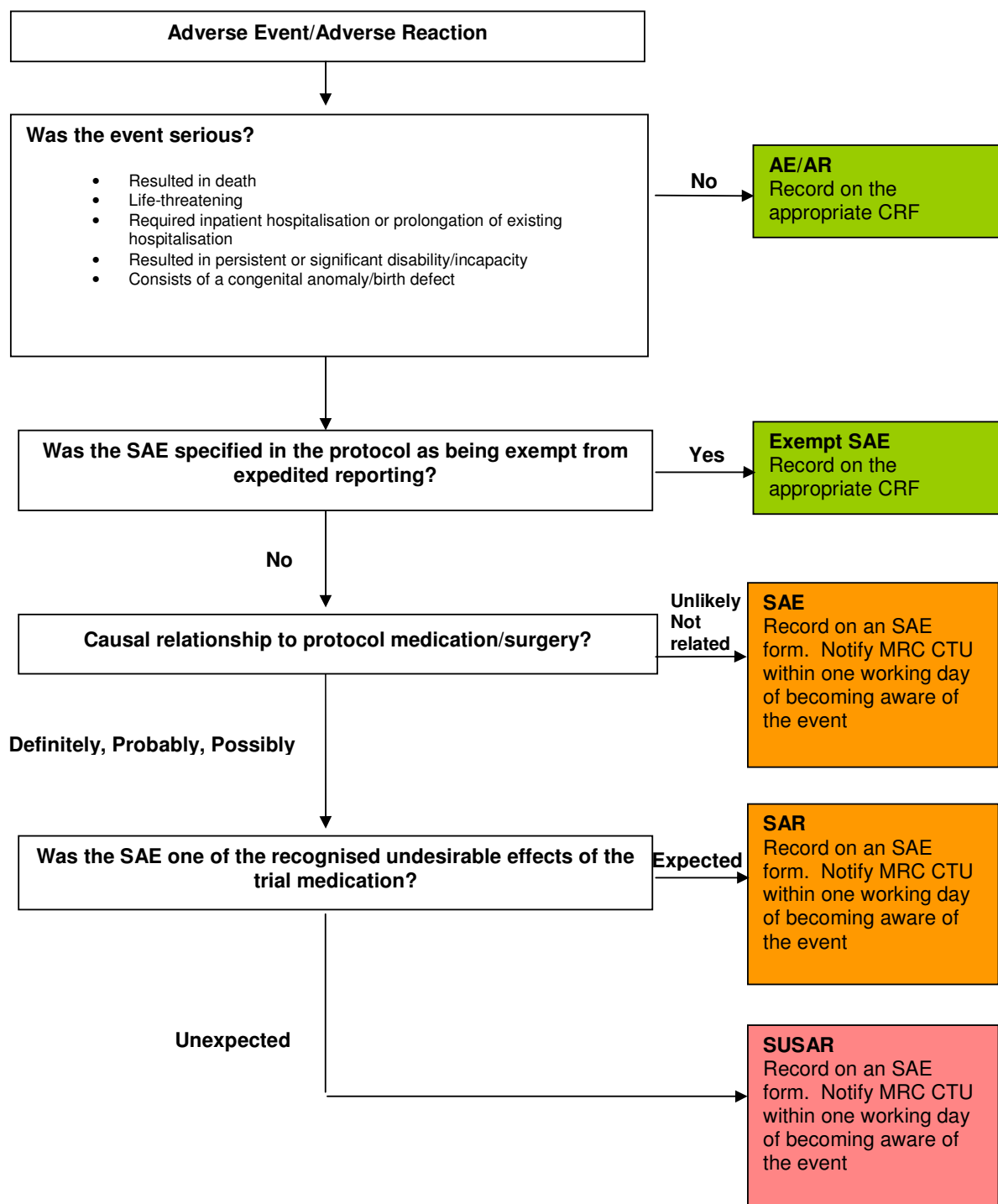
### *13.6 MRC CTU Responsibilities*

Medically qualified staff at the MRC CTU and/or the Chief Investigator (or a medically qualified delegate) will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor with respect to reporting of SUSARs and other SARs to the regulatory authority (MHRA) and the main REC.

The MRC CTU will inform investigators of any safety issues that arise during the course of the trial.

Figure 2: Safety Reporting Flowchart



**CRF:** Case Report Form  
**AE:** Adverse Event  
**AR:** Adverse Reaction

**SAE:** Serious Adverse Event  
**SAR:** Serious Adverse Reaction  
**SUSAR:** Suspected Unexpected Serious Adverse Reaction

## 14. Statistical Considerations

### 14.1 Method of randomisation

Patients will be randomly assigned to one of the two treatment groups in a 1:1 ratio. Minimization with a random element to ensure that the groups are well balanced with respect to 5 factors: randomizing centres, largest tumour size measured radiologically, clinical stage, chosen chemotherapy regimen and intention to perform debulking surgery.

### 14.2 Outcome Measures

The primary outcome measure of this trial is:

- Overall survival

Secondary outcome measures are

- Progression-free survival
- Quality of life
- Safety

Survival will be assessed from date of randomisation to date of death; surviving patients will be censored at date last known to be alive.

Progression-free survival will be assessed from date of randomisation to diagnosis of progression or death (from any cause). Details on definitions of progression can be found on Appendix C.

Quality of life is being assessed using the EORTC QLQ-C30 questionnaire and the QLQ-OV28 module. Comparisons will be made between arms at defined timepoints: after 3<sup>rd</sup> and 6<sup>th</sup> cycle of chemotherapy, and at 6 and 12 months after randomisation.

### 14.3 Sample size

CHORUS is designed to demonstrate that the neoadjuvant chemotherapy arm is not inferior to the primary surgery arm in terms of overall survival by combining the data with 704 patients from EORTC 55971 trial. We aim to accrue 400 patients in 4 years combined with 150 patients from the feasibility CHORUS study, giving a total of 550 patients. The sample size estimation is based on 2-year follow-up (minimum) after the completion of accrual. The 3-year overall survival rate is approximately 50-55% (based on data from ICON3 and taking into account more optimally debulked patients in EORTC 55971) in the primary surgery arm.

With 1250 patients randomised (550 CHORUS, 704 EORTC 55971) the trial will have 80% power to exclude a maximum difference of 5% (901 events required), or 90% power to exclude a maximum difference of 6% (868 events required) in 3-year overall survival with a significance level of 10% (one-sided).

### 14.4 Statistical Analysis Plan

A statistical analysis plan for the study to include detailed information on the analysis of primary and secondary outcome measures and plans for the prospective meta-analysis will be available on request from the MRC CTU.

## 15. Ancillary Studies

### 15.1 *Quality of Life*

Quality of life measurements are increasingly being used in randomised clinical trials to provide systematic, unbiased comparative data on patients' wellbeing, social and psychological functioning, their experience of disease symptoms and treatment-related side effects. As a considerable proportion of patients in the trial will relapse and die within 2 years, the impact that treatment has on their quality of life during this period is an important consideration. If neoadjuvant chemotherapy decreases mortality from ovarian, primary peritoneal, or fallopian tube cancer, the benefit will need to be considered in the context of the psychological and physical implications.

#### 15.1.1 INSTRUMENT

There are number of instruments available for assessing quality of life. We have chosen the EORTC QLQ-C30 questionnaire, a brief yet sensitive measure of quality of life for patient completion. The QLQ-C30 is a 30 item self-reporting questionnaire incorporating five functional scales (physical, role, cognitive, emotional and social), a global QL scale, three symptom scales (fatigue, pain and nausea & vomiting) and a number of single item measures. The questionnaire is widely used in trials worldwide and its practicality, validity and reliability have been well demonstrated.<sup>12,13</sup> In addition to the QLQ-C30 we shall also use the ovarian cancer module (QLQ-OV28) which is currently being developed by the EORTC quality of life trial group and is in the process of validation.

#### 15.1.2 COMPLETION OF QOL QUESTIONNAIRES

Given the poor prognosis for advanced ovarian cancer and hence the importance of treatment-related toxicity, all patients should be asked to complete a QLQ-C30 questionnaire and QLQ-OV28 module before randomisation, after the 3<sup>rd</sup> and 6<sup>th</sup> cycle of chemotherapy, and at 6 months and 12 months after randomisation. It should be emphasised that the completion of these forms helps doctors find out more about the effects of cancer treatment on patients' wellbeing. It is important to explain to the patient that the questions refer to how they have been feeling **during the past week**, and that **all** questions should be answered by circling the answer which is **closest** to the way they have been feeling.

The patient should be asked to complete the questionnaire, without conferring, whilst waiting to be seen in the clinic, in a quiet area if possible. The clinician or nurse in charge of the patient should collect the questionnaire before the patient leaves and should ask the patient to check that all questions have been answered. Patient privacy should be respected.

### 15.2 *Health Economics*

Within this trial, patients will be exposed to equivalent surgical and chemotherapeutic regimens, albeit at different times. Thus, it is not anticipated that costs should vary greatly. Some patients in the primary surgery arm may be considered for IDS by some clinicians, on the basis of clinical grounds, but this does not form part of this clinical trial. Health economics will therefore not be measured in this trial.

## 16. Ethical Considerations and approval

### 16.1 Ethical Considerations

This is a randomised controlled trial, therefore neither the patient nor the surgeon will be able to choose the patient's treatment. Treatment will be allocated randomly accruing to a computer-generated list. This is to ensure that the groups of patients allocated to the two arms are similar.

Prior to randomization, in some cases patients may have to have additional investigations to exclude gastro-intestinal cancer in order to comply with the eligibility criteria. Compared to the standard arm, patients randomised to the research arm will have to undergo an additional procedure to confirm that they do have ovarian, primary peritoneal or fallopian tube cancer. This has been balanced against the potential risk of administering inappropriate chemotherapy.

The trial will abide by the principles of the Declaration of Helsinki.

### 16.2 Ethical Approval

The protocol has the appropriate national research ethics committee (REC) approval for the countries in which it will be conducted.

Prior to allowing randomisation of any patient, each clinical centre must obtain local REC approval including approval of the local patient information sheet. Each patient's written consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment.

One copy of the signed form should be given to the patient, one copy should be filed with the patient's case notes and one copy should be filed in the Principal investigator site master file. With regard to quality of life, patients should receive a full explanation of the purposes of this part of the trial, the nature of the questionnaire and the frequency of completion.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if it is felt to be in the best interests of the patient. However, the reason for doing so should be recorded and the patient will need to remain within the trial for the purposes of follow-up and data analysis according to the treatment option she has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment, or from completion of the quality of life questionnaires, without giving reasons or prejudicing her future treatment.

A statement of MRC policy on ethical considerations in clinical trials of cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (<http://www.mrc.ac.uk>). This may be used to give guidance to participating investigators and to accompany applications to LREC.



### *16.3 Patient Confidentiality*

The MRC CTU is registered under the UK Data Protection Act to hold data as required for trial purposes. Trial databases will be held by MRC CTU. Patients will be allocated a unique trial number that will link all of the clinical information held about them on the trial databases. It will also be used in all correspondence with participating clinical trial sites. At no point in presentations or publications of trial data will individual patients be identified.

### *16.4 Regulatory Approval*

Investigators may not enrol patients to this trial without:

- The necessary notification or approval of the protocol and any amendments by the competent authority.
- The approval of the protocol and any amendments by the Ethics Committee/Institutional Review Board.

## **17. Sponsorship and Indemnity**

The MRC is the Sponsor of the trial.

The MRC accepts liability attached to its sponsorship and as such would give sympathetic consideration to claims for any non-negligent harm suffered by a subject as a result of participating in the trial. Like other publicly-funded bodies, any liability arising from the MRC's activities is underwritten by the UK Government and there is, therefore, no need to take out further cover for subjects participating in the trial.

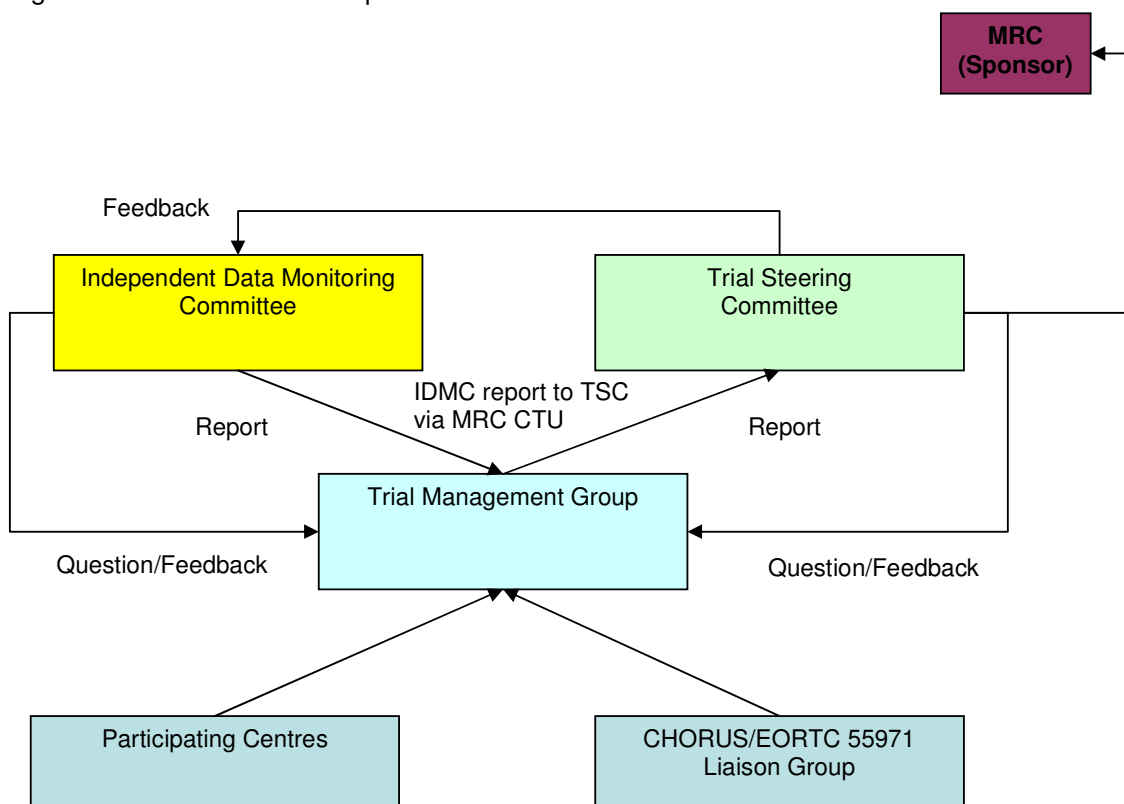
Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within that hospital, whether or not the patient is participating in an MRC-supported trial. Therefore, the MRC does not accept any liability for negligence on the part of employees of hospitals. This applies whether the hospital is a NHS Trust or not, and the MRC Cannot be held liable for any breach in the hospital's duty of care.

## **18. Finance**

The trial is coordinated at and by the MRC Clinical Trials Unit in London. Funding for the full trial has been obtained from Cancer Research UK.

## 19. Trial Committees

Figure 3 shows the relationships between the various trial committees



The Chief Investigators (CI) and the MRC CTU are responsible for the day to day running of the trial. The MRC CTU will prepare reports for the TMG, TSC and IDMC, including interim analysis, and will make safety and progress reports to the main REC and Medicines and Healthcare Products Regulatory Agency (MHRA).

**The Trial Management Group (TMG)** will receive regular updates on the trial and will aim to meet at least once per year. The TMG will advise the CIs and MRC CTU in the promotion and running of the trial. TMG members will review serious adverse events which have occurred in the trial. If there are specific safety concerns these may be raised with the TSC and IDMC. TMG members will include active trial investigators.

**Trial Steering Committee (TSC).** The MRC Gynaecology Trial Steering Committee has members who are independent of investigators and the MRC CTU while also including CTU staff working on the trial. It will provide overall supervision of the trial. It will meet at least annually, and will receive reports from the MRC CTU, TMG and IDMC.

**Independent Data Monitoring Committee (IDMC)** is independent of investigators and the MRC CTU. The group will meet at least once every year while patients are receiving trial treatment and thereafter as required. The IDMC will review reports from the MRC CTU and give advice on continuing recruitment. No formal stopping rules for efficacy are planned. A recommendation to discontinue recruitment (in all patients or in selected subgroups) will be made only if the emerging safety data indicate that the safety of the patients is not ensured. The IDMC will make recommendations to the TSC as to the

continuation of the trial. A copy of the IDMC charter is available from the MRC CTU on request.

Charters will be developed for all committees.

**CHORUS/EORTC 55971 Liaison Group** consisting of the Chief Investigators of CHORUS and EORTC 55971 and representatives of MRC CTU and EORTC Data Centre have met to ensure that similar data are being collected in both trials to enable a prospective meta-analysis and will continue to meet as required.

## 20. Publication

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of participants, and will acknowledge the role of all individuals in the trial and the role of the writing committee (which should include the Principal Investigator, Medical Oncology Advisor, Clinical Trial Manager(s), and Statistician(s) involved in the trial).

## 21. Protocol Amendments

Please check that you are using the most recent version of the CHORUS protocol.

The Chorus protocol had a non-substantial amendment on the 5<sup>th</sup> June 2008. The following changes were made:

- There were changes to the trial staff on the inside front cover.
- Section 6.1 was rewritten to clarify eligibility regarding clinical and imaging assessment, and that patient must be randomised within 6 weeks of imaging, to reflect standard practice within the trial.
- Section 7 on page 10 was changed regarding the collection of patient names. Patient names are no longer collected as standard practice.
- The wording in section 8.1, on page 12, was clarified to confirm that the histological/cytological disease confirmation may have been carried out before randomisation (for patients randomised to the neoadjuvant chemotherapy arm).

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  16. World Health Organization. WHO handbook for reporting results of cancer treatment. *WHO Offset Publication No. 48*, 1979.
  17. Talbot R.W., Jacobsen D.J., Nagorney D.M. *et al.* Temporary elevation of CA 125 after abdominal surgical treatment for benign disease and cancer. *Surgery, Gynecology and Obstetrics*, 1989; **168**: 407-412.

**APPENDIX A: CALCULATIONS FOR GFR AND CARBOPLATIN DOSE****Estimation and Measurement of Glomerular Filtration Rate for Calculation of Carboplatin Dose****Estimation and Measurement of Glomerular Filtration Rate (GFR)**

For the purposes of this protocol, the GFR can be considered equivalent to the creatinine clearance (CrCl). The following methods are suggested however it is advised that the centre calculates the GFR according to local guidelines:

- **Estimation of GFR using the Wright formula**

There are a number of different Wright formulae, depending on whether or not the creatinine kinase is available and used in the calculation, and also depending on how the serum creatinine is measured. The formula immediately below does not require a creatinine kinase measurement. This formula is also only valid if the laboratory measuring the serum creatinine uses the Jaffe method to do this. Centres will need to check with their local pathology laboratory how the serum creatinine is measured.

$$\text{GFR} = \frac{\{[6580 - (38.8 \times \text{age})] \times \text{BSA} \times 0.832\}}{\text{SCr}}$$

If the creatinine is measured using enzymic methods then following Wright formula should be used:

$$\text{GFR} = \frac{\{[6230 - (32.8 \times \text{age})] \times \text{BSA} \times 0.77\}}{\text{SCr}}$$

- **Estimation of GFR using the Jelliffe formula**

$$\text{GFR} = \frac{0.9 \times [98 - \{0.8(\text{age} - 20)\}] \times [\text{BSA}/1.73]}{\text{SCr} \times 0.0113}$$

- **Estimation of GFR using the Cockcroft-Gault formula**

$$\text{GFR} = \frac{1.05 \times (140 - \text{age}) \times \text{Wt}}{\text{SCr}}$$

Where	CrCl	=	Creatinine Clearance (ml/min)
	GFR	=	Glomerular Filtration Rate (ml/min)
	BSA	=	DuBois Body Surface Area (m <sup>2</sup> )
	SCr	=	Serum Creatinine (μmol/l)
	Wt	=	Weight (kg)
	Age	=	Age in years (20 to 80)

To convert serum creatinine in mg/dml to μmol/l use the following formula:

$$\text{Cr (μmol/l)} = \text{Cr (mg/dl)} \times 88.4$$

**Measurement of GFR**

A measured GFR is recommended if the serum creatinine is less than or equal to 53  $\mu\text{mol/l}$  (0.6 mg/dl) or the calculated GFR is  $< 60\text{ml/min}$ . The lower of the two values of creatinine clearance should be used to calculate dose. The GFR can be measured by

- **24 hour urine collection** or
- **Isotopic GFR** (using the value uncorrected for body surface area, BSA)

**APPENDIX B: RECOMMENDED DOSE MODIFICATIONS**

Whenever doses are modified or delayed a 3-weekly schedule should be resumed for subsequent cycles if possible. The following recommendations apply only to patients who have not been double randomised into SCOTROC4. For patients randomised to SCOTROC4 please follow the dose modification guidelines in the appropriate protocol.

**Single Agent Carboplatin****Haematological**

Blood counts must be measured immediately prior to each cycle. For patients enrolled in CHORUS only, treatment should be given on schedule if neutrophil count is  $\geq 1.5 \times 10^9/\text{l}$  and platelet count is  $\geq 100 \times 10^9/\text{l}$ .

In patients not achieving a neutrophil count of  $\geq 1.5 \times 10^9/\text{l}$  or a platelet count of  $\geq 100 \times 10^9/\text{l}$ , it is recommended that a one week delay in treatment should be instituted. If the haematological parameters have recovered after one week (i.e. neutrophils  $\geq 1.5 \times 10^9/\text{l}$ ; platelets  $\geq 100 \times 10^9/\text{l}$ ), treatment should continue at the same dose. If patients are required to delay for two weeks due to prolonged haematological toxicity then it is recommended that the dose of carboplatin should be reduced by 1 AUC unit (to AUC4 for patients dosed on isotopic GFR or AUC5 for those doses on calculated clearance).

All subsequent doses should remain at the reduced level. The use of G-CSF or a change from carboplatin to cisplatin is permitted according to local practice. If blood counts do not recover after two dose delays (i.e. two weeks), the patient should be taken off protocol treatment at the discretion of the clinician.

The patient should be advised that neutropenic fever may occur during the cycle and to seek medical advice if a high temperature or fever is experienced.

**Renal**

The GFR should be measured before the first cycle by  $^{51}\text{Cr}$ -EDTA clearance if possible. Subsequent doses of carboplatin would normally be based on this value of GFR. However, the GFR should be re-measured or re-calculated and the appropriate new dose of carboplatin prescribed in the following circumstances.

- Renal toxicity (CTC grade 2, serum creatinine  $>1.5 \times \text{ULN}$ )
  - Changes in serum creatinine of  $\geq 10\%$
  - Each dose modification of carboplatin
  - Cycle 2, if there has been significant doubt about the true GFR at cycle 1 (e.g due to significant ascites)
- 1- If the patient has been double-randomised into SCOTROC4 then a nadir blood count should be performed between days 14-18 as mandated. Dose modifications should be performed on the basis of this count following the guidelines given in the SCOTROC4 protocol (Pg 8)



## Paclitaxel And Carboplatin

### Haematological

Blood counts must be measured immediately prior to each cycle. Treatment should be given on schedule if neutrophil count is  $\geq 1.5 \times 10^9/l$  and platelet count is  $\geq 100 \times 10^9/l$ . In patients not achieving a neutrophil count of  $\geq 1.5 \times 10^9/l$  or a platelet count of  $\geq 100 \times 10^9/l$ , it is recommended that a one week delay in treatment should be instituted. If the haematological parameters have recovered after one week (i.e. neutrophils  $\geq 1.5 \times 10^9/l$ ; platelets  $\geq 100 \times 10^9/l$ ), treatment should continue at the same dose. If patients are required to delay for two weeks due to prolonged haematological toxicity then the recommended dose modifications are given below.

	Neutrophils $> 1.5 \times 10^9/l$	Neutrophils $\leq 1.5 \times 10^9/l$
Platelets $> 100 \times 10^9/l$	Carboplatin: 100% dose Paclitaxel: 100% dose	Carboplatin: 100% dose Paclitaxel: 75% dose
Platelets $\leq 100 \times 10^9/l$	Carboplatin reduce by 1 AUC unit (AUC to 4 if using isotopic GFR and 5 if using calculated clearance) Paclitaxel: 100% dose	Carboplatin reduce by 1 AUC unit (AUC to 4 if using isotopic GFR and 5 if using calculated clearance) Paclitaxel: 75% dose

All subsequent doses should remain at the reduced level. The use of G-CSF or a change from carboplatin to cisplatin is permitted according to local practice. If blood counts do not recover after two dose delays (i.e. two weeks), the patient should be taken off protocol treatment at the discretion of the clinician.

The patient should be advised that neutropenic fever may occur during the cycle and to seek medical advice if a high temperature or fever is experienced.

### Neuropathy

If patients describe Grade 2 sensory or motor neuropathy, paclitaxel should be reduced in **all** subsequent cycles to  $135\text{mg}/\text{m}^2$ . If progressive neuropathy is observed after this dose reduction then treatment with paclitaxel should be discontinued. If patients describe  $\geq$  grade 3 neuropathy, paclitaxel should be discontinued.

### Hypersensitivity

A hypersensitivity reaction to paclitaxel is not a dose-limiting toxicity. The acute management should be as per local practice.

Hypersensitivity is not a contraindication to paclitaxel and patients may be retreated at full dose at the discretion of the investigator. If re-treatment is felt to be beneficial despite a hypersensitivity reaction, the following re-challenge schedule may be adopted:

Dexamethasone 20mg iv given the night before chemotherapy, 20mg given with breakfast on the day of chemotherapy and 20mg iv 30 minutes prior to paclitaxel.

Ranitidine 50mg iv or cimetidine 300mg stat 30 minutes prior to paclitaxel

Chlorpheniramine 10mg iv stat 30 minutes prior to paclitaxel

Paclitaxel given at 10% of the rate needed to give the solution over 3 hours i.e. approximately  $16\text{ml}/\text{hour}$ . If no further reaction is seen within 2 hours, then the

rate can be increased to 32ml/hour for one hour, then 64ml/hour for one hour, then 120ml/hour for one hour and finally back to the standard 166ml/hour. Each escalation of rate should only be undertaken if no hypersensitivity has been seen in the previous hour

Emergency resuscitation equipment and personnel should be available during the period of re-challenge.

If the re-challenge is occurring within 72 hours of the original intended dosing, and a negligible quantity *i.e.* 50ml or less of the original dose was administered, re-administer the full dose. If a substantial proportion (*i.e.*  $\geq 10\%$  total dose) has been given the balance of the full original dose should be re-administered.

If the re-challenge is being considered more than 72 hours after the original intended dosing then a full blood count should be taken to check suitability.

**Renal**

Carboplatin and paclitaxel using the schedule previously described is not expected to cause renal toxicity. There are therefore no specific dose modifications for renal toxicity, however the administered dose of carboplatin must be recalculated, based on a recalculated or re-measured GFR for

- Renal toxicity (CTC grade 2, serum creatinine  $>1.5 \times \text{ULN}$ )
- Changes in serum creatinine of  $\geq 10\%$
- Each dose modification of carboplatin
- Cycle 2, if there has been significant doubt about the true GFR at cycle 1 (e.g due to significant ascites)

**APPENDIX C: EVALUATION CRITERIA OF DISEASE STATUS****DEFINITION OF PROGRESSION (based on WHO Criteria<sup>16</sup>)**

Progression is defined as ANY of the following:

- An estimated increase of 25% or more in tumour masses documented at baseline
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression

After completion of protocol-directed treatment, progression can also be based upon serum CA 125 as follows:

- Patients with elevated CA 125 pretreatment and normalisation of CA 125 must show evidence of CA 125 greater than or equal to two times the upper normal limit on two occasions at least one week apart **or**
- Patients with elevated CA 125 pretreatment, which never normalises must show evidence of CA 125 greater than or equal to two times the nadir value on two occasions at least one week apart **or**
- Patients with CA 125 in the normal range pretreatment must show evidence of CA 125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

**Please note:-**

**Due to the potential for false-elevations of CA 125 levels secondary to surgical or medical disturbance to the peritoneum, CA 125 levels within 4 weeks after surgery should not be taken into account.<sup>17</sup>**

**Patients with elevations of CA 125 during treatment should continue to receive protocol-directed treatment; however, clinicians are encouraged to perform additional assessments (e.g. physical examination, radiographic imaging) in order to exclude clinical or radiological progression. In the event of clinical or radiological progression, protocol-directed treatment may be stopped.**

**APPENDIX D: WHO PERFORMANCE STATUS**

0 = Normal activity without restriction

1 = Strenuous activity restricted, can do light work

2 = Up and about > 50% of waking hours, capable of self-care

3 = Confined to bed >50% of waking hours, limited self care

4 = Confined to bed or chair, no self-care, completely disabled

**APPENDIX E: FIGO STAGING (OVARIAN CANCER)****Stage**

- I** Growth limited to the ovaries
  - Ia** Growth limited to one ovary; no ascites. No tumour on the external surfaces; capsule intact
  - Ib** Growth limited to both ovaries; no ascites. No tumour on the external surfaces; capsule intact
  - Ic** Tumour either Stage Ia or Ib, but with tumour on surface on one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings

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- II** Growth involving one or both ovaries with pelvic extension
  - Ila** Extension and/or metastases to the uterus and/or tubes
  - Ilb** Extension to other pelvic tissues
  - Ilc** Tumour either Stage IIa or IIb, but with tumour on surface on one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings

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- III** Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumour is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum
  - IIla** Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of the peritoneal surfaces
  - IIlb** Tumour involving one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces nodes none exceeding 2cm in diameter. Nodes are negative
  - IIlc** Abdominal implants greater than 2cm in diameter and/or positive retroperitoneal or inguinal nodes

---

- IV** Growth involving one or both ovaries with distant metastases. If pleural effusion is present there must be positive cytology to allot a case to Stage IV

**APPENDIX F: LIST OF EXPECTED TOXICITIES**

Toxicities/side effects that have previously occurred and are listed in the SPC are listed here. Please record all side effects on the chemotherapy form. These will not have to be reported to the MHRA but will be collected as toxicity is an endpoint of the trial. If the outcome of the side effect is serious (see CHORUS protocol for definitions), the Serious Event Reporting Form should **also** be completed. Any toxicity not described below, i.e. a toxicity that is unexpected, will be reported as a SUSAR.

<b>Toxicity</b>	<b>Carboplatin</b>	<b>Paclitaxel</b>
<b>Haemopoietic:</b>		
Anaemia	✓	✓
Febrile neutropenia	✓	✓
Grade 3 or 4 lab abnormalities (according to CTC v3.0)	✓	✓
Leukopenia	✓	✓
Neutropenia	✓	✓
Thrombocytopenia	✓	✓
<b>Gastrointestinal or Hepatobiliary:</b>		
Abdominal pain / cramps	✓	No
Anorexia	No	✓
Ascites	No	✓
Constipation	✓	✓
Diarrhoea (including fatal diarrhoea) / Loose stools	✓	✓
Gastrointestinal ischaemia (including fatal) (including mesenteric vein thrombosis, and/or causing enteritis/ colitis / proctitis)	No	✓
Gastrointestinal obstruction (large and small bowel) ± dilatation	No	✓
Gastrointestinal perforation (large or small bowel or gallbladder)	No	✓
Hepatic failure (including encephalopathy, fatal and long term)	No	✓
Nausea	✓	✓
Oesophagitis/ gastritis/ enteritis / colitis (inc Clostridium difficile colitis) / caecitis	No	✓
Pancreatitis	No	✓
Stomatitis / mucositis / mouth ulceration	No	✓
Taste disturbance / Dysgeusia	✓	No
Vomiting	✓	✓
<b>Neurotoxicity:</b>		
Asthenia / fatigue	No	✓
Ataxia	No	✓
Autonomic neuropathy	No	✓
Confusional state	No	✓
Convulsion	No	✓
Dizziness	No	✓
Encephalopathy	No	✓
Headache	No	✓

<b>Toxicity</b>	<b>Carboplatin</b>	<b>Paclitaxel</b>
Ototoxicity (hearing loss and/or tinnitus and/or vertigo)	✓	✓
Peripheral neuropathy (sensory and/or motor) /	✓	✓
Transient visual disturbance / blindness	✓	✓
<b>Biochemistry</b>		
Elevated alkaline phosphatase (including grade 3 or 4	✓	✓
Elevated ALT (including grade 3 or 4 [CTC v3.0])	✓	✓
Elevated AST (including grade 3 or 4 [CTC v3.0])	✓	✓
Elevated bilirubin (including grade 3 or 4 [CTC v3.0])	✓	✓
Hyperuraemia	✓	No
Hyperuricaemia	✓	No
<b>Cardiovascular:</b>		
Angina pectoris / Myocardial ischaemia / Myocardial Infarction (MI) (fatal)	No	✓
Arrhythmia (ventricular and supraventricular, including atrial fibrillation) (fatal)	No	✓
Bradycardia	No	✓
Cardiomyopathy	No	✓
Deep vein thrombosis	No	✓
Embolic event (peripheral or pulmonary)	No	✓
Hypertension (including hypertensive crisis or hypertensive encephalopathy)	No	✓ (milder)
Hypotension	No	✓
Peripheral oedema	No	✓
Thrombophlebitis	No	✓
<b>Cutaneous:</b>		
Alopecia	✓	✓
Epidermal necrolysis	No	✓
Erythema multiforme	No	✓
Exfoliative dermatitis	No	✓
Nail changes including onycholysis	No	✓
Rash	✓	✓
Skin discolouration	No	✓
Stevens-Johnson syndrome	No	✓
<b>Respiratory effects:</b>		
Cough	No	✓
Dyspnoea	✓	✓
Interstitial pneumonitis	No	✓
Pleural effusion / malignant pleural effusion	No	✓
Pulmonary fibrosis (rare)	✓	✓
Respiratory distress (long term)	✓	No
Respiratory failure	No	✓
<b>Gynaecological and Urological effects:</b>		
Renal impairment / failure	✓	✓
<b>General undesirable effects:</b>		
Acute myeloid leukaemia	No	✓
Drug hypersensitivity / anaphylactic reaction	✓	✓

<b>Toxicity</b>	<b>Carboplatin</b>	<b>Paclitaxel</b>
Arthralgia	✓	✓
<b>General undesirable effects / miscellaneous:</b>		
Chills / pyrexia	No	✓
Dehydration	No	✓
Flu-like syndrome	✓	
Injection site reaction	✓	✓
Infection / sepsis (fatal) (including wound infection) / abscess	✓	✓
Myalgia	No	✓
Myelodysplastic syndrome	No	✓



## Intergroup Study (EORTC 55971/NCIC OV13)

**Randomized Phase III study comparing upfront  
debulking surgery versus neo-adjuvant chemotherapy  
in patients with Stage IIIc or IV epithelial ovarian  
carcinoma**

**Amendment 8 + Administrative change 2**

**Coordinating Group:**

**EORTC Gynecological Cancer Group**

**Collaborative Group:**

**National Cancer Institute of Canada (NCIC)**

**Study Chairman: Pr. Ignace Vergote**

Date	Subject	Version	New numbering system
21/07/1997	PRC outline approval		
13/07/1998	PRC Full Protocol approval	16/09/1998	1.0
10/12/1998	PRC amendment 1 approval	29/03/1999	2.0
29/01/1999	PRC amendment 2 approval	29/03/1999	3.0
07/07/1999	PRC amendment 3 approval	AM3PR0799	4.0
07/07/1999	PRC amendment 4 approval	30/06/1999	5.0
10/07/2000	PRC amendment 5 approval	Am5protocoljuly2000	6.0
19/11/2001	PRC administrative change 1 notification	5.1 November 2001	6.1
23/04/2002	PRC amendment 6 approval	6.1 May 2002	7.0
24/05/2002	PRC amendment 7 approval	7.1 May 2002	8.0
20/02/2003	PRC amendment 8 approval	9.0	9.0
06/10/2003	Administrative change 2	9.1	9.1

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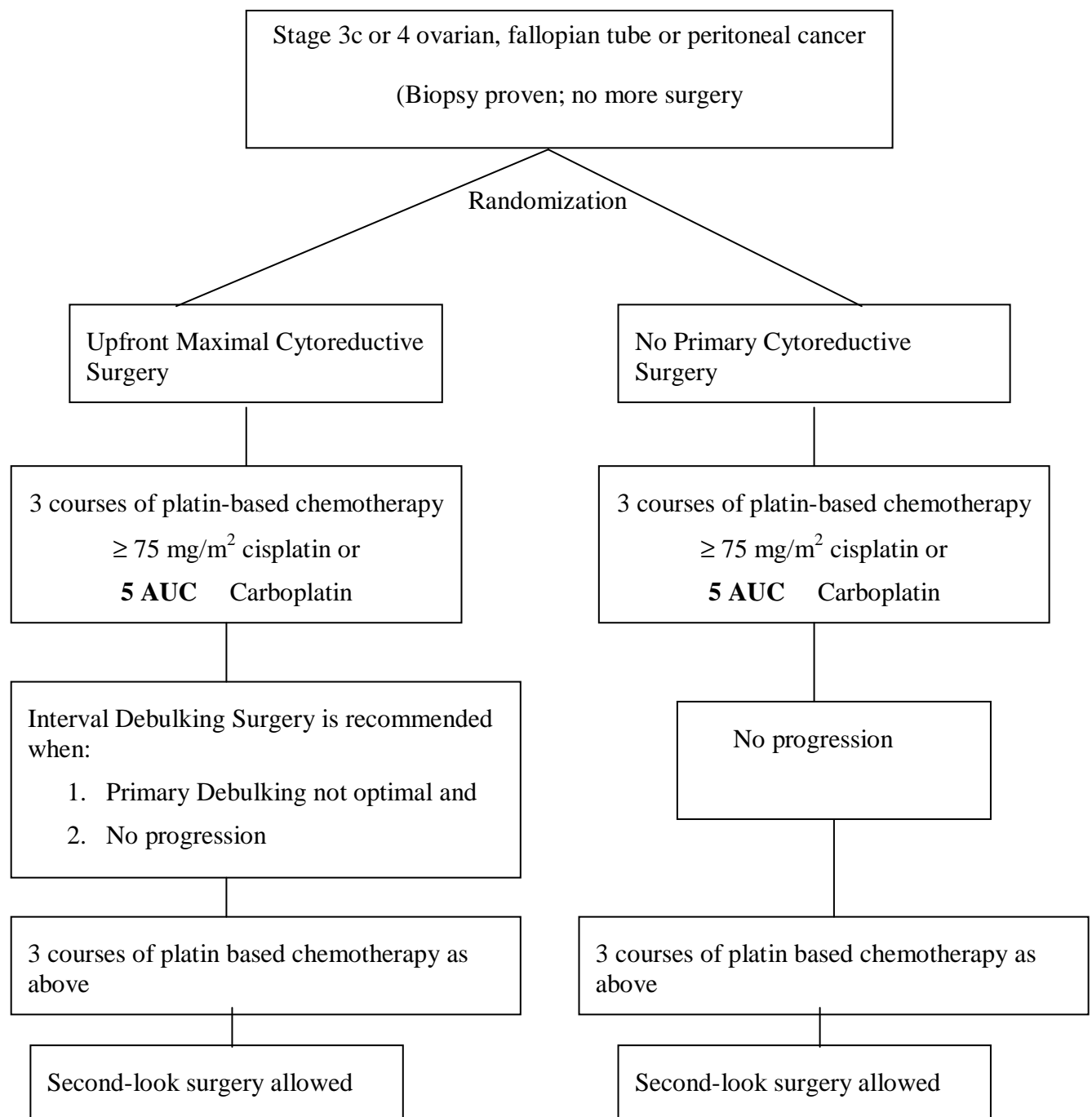
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## 1. BACKGROUND AND INTRODUCTION

Virtually all studies of advanced ovarian carcinoma demonstrated that the size of residual tumor prior to the initiation of chemotherapy was an important determinant of prognosis in advanced ovarian carcinoma (Stage III and IV) <sup>1-8</sup>. Present practice in such situations in many institutions is to optimally “debulk” the tumor. Unfortunately, no prospective randomized controlled trials concerning the role of *primary* cytoreductive surgery in advanced ovarian carcinoma have been performed. In the past 20 years the definition of an “optimal debulking” has changed many times, going from a largest residual tumor mass of 2 cm to no residual tumor. Using the authors’ definition of “optimal” debulking, it has been shown that the median survival is 39 and 17 months, respectively, for patients who have undergone successful surgical cytoreduction compared with patients with “suboptimal” residual disease <sup>9</sup>. Based on these data the general opinion is that in patients in whom the tumor *cannot be optimally debulked*, cytoreductive surgery to larger lesions does not improve survival. The problem still fiercely under debate is whether the observed survival benefits for cytoreduced patients are a function of surgical skill, tumor biology or both. Indirect evidence is available that inherent tumor biology relates to resectability <sup>9-12</sup>. Many retrospective studies showed that the prognosis in debulked patients is related to other factors than residual disease such as the amount of tumor in the upper abdomen prior to surgery <sup>9,10,13,14</sup>, the presence of ascites <sup>10,14</sup>, age, poor degree of differentiation <sup>15</sup>, and the presence of uncountable peritoneal metastases <sup>9,16,17</sup>. All these studies hamper the unavoidable bias comparing patients with different prognostic factors.

The only randomized trial on cytoreductive surgery was performed by the EORTC-GCCG and showed that *interval* cytoreductive surgery after 3 courses of platin-based chemotherapy lengthened progression-free and overall survival in the group of patients that could not be cytoreduced primarily <sup>18</sup>. Even in patients with a suboptimal debulking surgery the tumor reduction showed a survival benefit. Based on these data one could conclude that also at primary surgery tumor reduction, even when in patients with suboptimal cytoreduction results in a survival benefit. On the contrary recently neoadjuvant chemotherapy has been proposed in patients with established bulky disease <sup>19-23</sup>. In one retrospective study the survival of a group of patients (n = 174) with advanced ovarian carcinoma treated neo-adjuvant chemotherapy when unfavorable characteristics were present was similar to a former series (n = 112) treated at the same institution with “optimal” debulking (<1.5 cm) in 89% of the patients <sup>23</sup>. The studies suggest that the same survival with a lower operative morbidity might be obtained with neoadjuvant chemotherapy compared with primary cytoreductive surgery. Nelson proposed computerized tomographic criteria to predict operability in patients with suspect ovarian masses <sup>24</sup>. Another possibility is to perform an (open) laparoscopy to confirm the diagnosis and to evaluate the operability <sup>25</sup>.

In this prospective study patients with Stage IIIC or IV ovarian carcinoma will be randomized to neoadjuvant chemotherapy followed by interval debulking surgery or primary debulking surgery followed by chemotherapy with or without interval debulking surgery.

## 2. OBJECTIVES OF THE TRIAL

The main question to be answered by this protocol is whether neo-adjuvant chemotherapy followed by interval debulking surgery has the same survival compared with upfront debulking surgery followed by postoperative chemotherapy, and analyzing whether this approach results in a lower postoperative morbidity and improved quality of life.

The primary endpoint is overall crude survival.

The secondary endpoints are:

1. Progression-free survival.
2. Quality of life according to the EORTC questionnaire QLQ-C30
3. To assess the different treatment complications in relation to treatment arm.

### 3. PATIENT SELECTION CRITERIA

1. Preferentially biopsy proven Stage IIIc or IV epithelial ovarian carcinoma, or peritoneal or fallopian tube carcinoma. If biopsy is not available, fine needle aspiration (FNA) showing an adenocarcinoma is acceptable under the following conditions:

- ♦ the patient has a pelvic (ovarian) mass, AND
- ♦ omental cake or other metastasis larger than 2 cm in the upper abdomen and/or regional lymphnode metastasis irrespective of size, or stage IV AND
- ♦ serum CA125/ CEA ratio  $> 25$  (ref 42). If the serum CA125/CEA ratio is  $< 25$ , a barium enema (or colonoscopy) and gastroscopy (or radiological examination of the stomach) should be negative for the presence of a primary tumor ( $< 6$  weeks before randomization), and normal mammography ( $< 6$  weeks).

2. WHO performance status of 0, 1, or 2.

3. No other serious disabling diseases contraindicating for primary cytoreductive surgery or primary platin based chemotherapy.

4. No other prior primary malignancies, except for carcinoma in situ of the cervix and basal carcinoma of the skin.

5. No clinical evidence of brain or leptomeningeal metastases.

6. Adequate hematological, renal and hepatic function to permit platin- *paclitaxel* based chemotherapy: WBC  $> 3.0 \times 10^9/L$ , platelets  $> 100 \times 10^9/L$ , serum creatinine  $< 1.25 \times$  upper normal range, serum bilirubin  $< 1.25 \times$  upper normal range.

7. Absence of any psychological, familial, sociological or geographical condition potentially preventing compliance with the study protocol and follow-up schedule; those conditions should be assessed with the patient before registration in the trial.

8. Before patient registration/randomization, informed consent must be obtained and documented according to national and local regulatory requirements and the local rules followed in the institution.

### 4. TRIAL DESIGN.

For schema see page 3.

**Diagnosis:** 1. Intraperitoneal biopsy taken with the help of laparoscopy, laparotomy, imaging-guidance or Fine Needle Aspiration should prove the presence of epithelial ovarian, peritoneal or fallopian tube carcinoma. Patients who undergo laparotomy or laparoscopy should not have had any other procedure than the diagnostic biopsies.

AND

2. Presence of a tumor larger than 2 cm (**excluding ovaries**) on laparoscopy or CAT scan.

**Treatment:** Randomization to:

**Arm A:** Upfront maximal cytoreductive surgery followed by 3 courses of platin based chemotherapy (for details see Section 5). *Immediately after surgery, patient must be randomized in trial 55012 (if intended to randomize patients in both trials).* Interval debulking surgery is recommended but can be performed at physician's discretion in patients with non-optimal primary debulking surgery and again at least 3 courses of platin based chemotherapy (same regimen as before the interval debulking surgery).

**Arm B:** Three courses of chemotherapy as in arm A followed by interval debulking surgery in all patients with response or stable disease. *Immediately after randomization to this arm, patient must be randomized in trial 55012 (if intended to randomize patients in both trials).* Followed again by at least 3 courses of platin based chemotherapy (same regimen as before the interval debulking surgery). For details see section 5.

**Stratification:**

1. Institution.
2. Method of biopsy (laparoscopy, imaging-guidance or laparotomy, FNA).
3. FIGO Stage IIIc or IV (Appendix 3)
4. Largest tumor size (**excluding ovaries**) before surgery of 2 - 5 cm, 5 - 10 cm, 10 - 20 cm, > 20 cm. The tumor size is preferentially measured during surgery and if not done based on CT findings.
5. Intention to randomize the patient also in the 55012 trial

**Principal surgeon.** Only senior surgeons will be allowed to have the responsibility for the primary, interval or second-look surgery. Each institution will have to appoint their senior surgeons prior to starting the study. Each senior surgeon will follow carefully the guideline for surgery as mentioned in appendix 4. This will be checked by an on-site visits.

**Second-look surgery:** Each institution will have to declare before starting the study, whether they will perform second-look surgery or not in their patients. This policy must be adhered to for all patients included in both arms.

**Percentage of optimal primary debulking.**

As stated in the statistics it is expected that about 50% randomized to primary debulking surgery will have a optimal debulking. Each year the percentage of optimal debulking procedures will be computed by the EORTC Data Center and discussed with the Independent Monitoring Committee which might consequently advise to redefine the required number of patients.



## 5. THERAPEUTIC REGIMENS.

- Arm A:**
- a. Upfront maximal cytoreductive surgery within 3 weeks after biopsy (see diagnosis) Immediately after surgery, patient must be randomized in trial 55012 (if intended to randomize patients in both trials)
  - b. Followed within 3 weeks by 3 courses of chemotherapy. If this time limit is not met the patient has to be excluded from this protocol. Chemotherapy should be an cisplatin (starting dose of at least 75 mg/m<sup>2</sup>/3 weeks, or other schedules containing a minimum of 25 mg/m<sup>2</sup> per week) or carboplatin-containing regimen (**dose of AUC 5 based on EDTA or Iohexol determination or, if not feasible (than omitted) Cockcroft or Chatelut formula**) The recommended regimens are summarized in Appendix 2.
  - c. Interval debulking surgery is recommended but can be performed at physician's discretion in patients with non-optimal primary debulking surgery (i.e. at least in all patients with > 1 cm largest residual tumor following primary surgery). Interval debulking surgery should be performed within 6 weeks after course 3 in all patients with response or stable disease. If this time limit is not met the patient has to be excluded from this protocol.
  - d. Followed by at least 3 courses of chemotherapy within 3 weeks after surgery as in b.
  - e. Second-look surgery is allowed if clinically indicated.
- Arm B:**
- a. 3 courses of chemotherapy as in arm A, initiated within 3 weeks after biopsy. Immediately after randomization to this arm, patient must be randomized in trial 55012 (if intended to randomize patients in both trials)
  - b. Interval debulking surgery should be performed within 6 weeks after course 3 in all patients with response or stable disease. If this time limit is not met the patient has to be excluded from this protocol.
  - c. Followed by at least 3 courses of chemotherapy within 3 weeks following surgery as in a.
  - d. Second-look surgery is allowed if clinically indicated.

**Each institution must choose for a policy (and declare this on the New Commitment form) before the inclusion of the first patient:**

**1. To follow one of the recommended regimens (see Appendix 2) for all patients. If another (not recommended) regimen is chosen this should be approved by the study coordinator. If an institution wishes to change the used regimen in their patients during the accrual of the protocol this has also to be approved by the study coordinator.**

2. each investigator may also decide to simultaneously include patients in both trials, 55971 and 55012. In such a case, either all eligible patients will be randomized in both trials, or only specific subgroup(s). This should be communicated to the study coordinator and to the respective Data Center and will be regularly checked by the respective Data Center.

## **6. CLINICAL EVALUATION, LABORATORY TESTS, FOLLOW-UP AND CRITERIA OF EVALUATION.**

Clinical evaluation, laboratory test and follow-up are summarized in Table 1 and 2:

TABLE 1. ARM A. Primary Debulking Surgery.

	Inclusion	Primary Debulking	Course 1 d1	Course 2 d1	Course 3 d1	Interval Debulking <sup>£</sup>	Course 4 d1	Course 5 d1	Course 6 d1	Second- look <sup>&amp;</sup>	Follow-up <sup>§</sup>
Check inclusion criteria	x										
WHO Performance status (APP 7)	x	x <sup>*</sup>	x	x	x	x <sup>*</sup>	x	x	x	x <sup>*</sup>	x
Serum <sup>μ</sup>	x <sup>ç</sup>	x <sup>*</sup>	x	x	x	x <sup>*</sup>	x	x	x	x <sup>*</sup>	
QOL-C30 <sup>**</sup>		x <sup>*</sup>			x (d20)				x (d20)		x (after 6 and 12 mths)
Tumor tissue for basic research <sup>&amp;</sup>		x <sup>&amp;</sup>				x <sup>&amp;</sup>				x <sup>&amp;</sup>	
Surgical form		x				x				x	
Postoperative complications		x (first 4 weeks)				x (first 4 weeks)				x (first 4 weeks)	
Tumor measurement (preferentially CT abdomen)	x		x <sup>*</sup>		x (day 14-21)		x <sup>*!</sup>		x (day 14-21)		

\* Maximal 1 week before; £. Recommended when primary surgery not optimal and in addition stable disease or response on chemotherapy;

& Optional; μ Serum: Leukocytes, neutrophiles, thrombocytes, hemoglobin, creatinine, bilirubin, Mg<sup>++</sup> Optional: CA125

ç CA125 and CEA recommended; In case of elevated CEA are endoscopic or radiologic examination of stomach and colon recommended.

\$ To be sent to Oncotech, USA, with the schemes and payment by Oncotech.

§ Follow-up every 3 months the first 2 years; every 6 months year 3 - 5; yearly afterwards.

**\*\* QOL: For patients simultaneously randomized in 55012, follow schedule of 55012**

! Only if interval debulking surgery performed

TABLE 2. ARM B. Neoadjuvant Chemotherapy.

	Inclusion	Course 1 d1	Course 2 d1	Course 3 d1	Interval Debulking <sup>£</sup>	Course 4 d1	Course 5 d1	Course 6 d1	Second- look <sup>&amp;</sup>	Follow-up <sup>§</sup>
Check inclusion criteria	x									
Performance status	x	x	x	x	x <sup>*</sup>	x	x	x	x <sup>*</sup>	x
Serum <sup>µ</sup>	x <sup>ç</sup>	x	x	x	x <sup>*</sup>	x	x	x	x <sup>*</sup>	
QOL-C30**		x		x (d20)				x (d20)		x (after 6 and 12 mths)
Tumor tissue for basic research <sup>&amp;</sup>					x <sup>&amp;</sup>				x <sup>&amp;</sup>	
Surgical scheme					x				x	
Postoperative complications					x (first 4 weeks)				x (first 4 weeks)	
Tumor measurement (preferentially CT abdomen)		x <sup>*</sup>		x (day 14-21)				x (day 14-21)		

\* Maximal 1 week before.

£. Only when stable disease or response on chemotherapy.

& Optional

µ Serum: Leukocytes, neutrophiles, thrombocytes, hemoglobin, creatinine, bilirubin, Mg<sup>++</sup>; optional: CA125.

ç CA125 and CEA recommended; In case of elevated CEA are endoscopic or radiologic examination of stomach and colon recommended.

\$ To be sent to Oncotech, USA, with the schemes and payment by Oncotech.

§ Follow-up every 3 months the first 2 years; every 6 months year 3 - 5; yearly afterwards.

\*\* QOL: For patients simultaneously randomized in 55012, follow schedule of 55012

**Clinical or radiological response.** Radiological examinations or eventually physical examinations can be used to determine the tumor size may be used but should be identical during the first-line chemotherapy. The assessment of response involves all parameters. The poorest response designation shall prevail and if progressive disease occurs at one site then the overall result will be progressive disease.

- a. Complete response (CR). Disappearance of all known disease, determined by 2 observations not less than 4 weeks apart.
- b. Partial response (PR) In the case of bi-dimensionally measurable disease, decrease by at least 50% of the sum of the products of the largest perpendicular diameters of the lesions which have been measured to determine the effect of therapy by 2 evaluations not less than 4 weeks apart. For uni-dimensional measurable lesions, decrease by at least 50% in the sum of the largest diameters of all lesions as determined by 2 evaluations not less than 4 weeks apart. It is not necessary for all lesions to qualify for partial response, but no lesions should have progressed or no new lesion should appear.
- c. Stable Disease (SD) A  $\geq 50\%$  decrease in the sum of the products of the largest perpendicular diameters (bi-dimensionally measurable disease) or largest diameters (uni-dimensionally measurable disease) of all lesions cannot be established nor can a progression as defined below be established.
- d. Progressive disease (PD) A  $\geq 25\%$  increase in the size of one or more bi- or uni-dimensionally measurable disease or appearance of a new lesion. The occurrence of cytologically malignant ascites or pleural fluid is also considered as PD.

### CA125 response evaluation. <sup>26-29</sup>

- a. 50% response is defined as a 50% decrease in serum CA125 levels. There must be 2 initial elevated samples followed by a third sample showing a 50% fall. The samples showing a 50% fall must be confirmed by a fourth sample (i.e. requires 4 CA125 samples). The final sample has to be analyzed at least 28 days after the previous sample.
- b. 75% response. A 75% response has occurred if there has been a serial decrease in serum CA125 levels of more than 75% over 3 samples (i.e. requires 3 CA125 levels). The final sample has to be analyzed at least 28 days after the previous sample.
- c. CA125 Stable disease. The criteria for 50% response, 75% response or CA125 progression are not (yet) fulfilled.
- d. CA125 disease progression. Disease progression based on CA125 relies on at least 3 samples. One of the following criteria must be fulfilled.

1. *Patients with CA125  $\leq 30$  KU/L.* Progression is defined by 2 consecutive samples  $> 60$  KU/L.

2. *Patients with CA125  $> 30$  KU/L.* Progression according to CA125 has occurred if there has been either:

- ◆ A 25% increase of a third sample compared with the 2 former samples which is confirmed by a 4th sample, or
- ◆ A 50% serial increase in CA125 over 3 samples, or

- ◆ A persistent elevation of CA125 over 100 KU/L for more than 56 days without a 50% decrease. At least 3 samples are needed.

**Surgical evaluation.** Evaluation at interval debulking, second-look or later surgery refers to prior surgical findings. The assessment of response involves all parameters. The poorest response designation shall prevail and if progressive disease occurs at one site then the overall result will be progressive disease.

a. Pathological Complete response (pCR). Disappearance of all known disease noted on prior surgery; all biopsies are microscopically negative.

b. Surgical Partial response (sPR). In the case of bi-dimensionally measurable disease, decrease by at least 50% of the sum of the products of the largest perpendicular diameters of the lesions which have been measured on prior surgery. For uni-dimensional measurable lesions, decrease by at least 50% in the sum of the largest diameters of all lesions as determined bat prior surgery. It is not necessary for all lesions to qualify for partial response, but no lesions should have progressed or no new lesion should appear. In case of macroscopically negative but microscopic positive disease the patient is classified as sPR.

c. Surgical Stable Disease (sSD). A  $\geq 50\%$  decrease in the sum of the products of the largest perpendicular diameters (bi-dimensionally measurable disease) or largest diameters (uni-dimensionally measurable disease) of all lesions cannot be established nor can a progression as defined below be established.

d. Progressive disease (sPD). A  $\geq 25\%$  increase in the size of one or more bi- or uni-dimensionally measurable disease or appearance of a new lesion. The occurrence of cytologically malignant ascites is also considered as sPD.

**Time to progression** will be defined as the time to clinically, CA125 or surgically defined PD as defined above, whichever occurs first.

**Overall survival** is defined as the time from randomization to the time of death of any cause. Overall survival will be censored at the last follow-up assessment at which the patients was known to be alive.

**Performance status** is evaluated according to the WHO criteria (See appendix 7).

**Toxicity of chemotherapy** will be evaluated according to the NCIC Common toxicity criteria (See Appendix 8). The worst level of each toxicity encountered by each patient will be reported.

**Toxicity of surgery** will also be reported according to the NCIC Common toxicity criteria and will be separately recorded for each surgery.

## 7. PATIENT REGISTRATION PROCEDURE

Patients registration/randomization will only be accepted from authorized investigators.

A patient can be registered / randomized after verification of eligibility directly on the EORTC Data Center computer, 24 hours a day, 7 days a week, through the Eurocode or the INTERNET network.

Alternatively registration/randomization can be done by telephone to the EORTC Data Center from 9.00 am to 6.00 p.m. Monday through Friday.

This must be done **before the start of the treatment.**

Telephone: (32 2) 774 16 00

EuroCODE (modem): (32 2) 772 04 26

EuroCODE (X25): (206) 221 51 24

Internet: telnet ecvax.eortc.be

<http://www.eortc.be/eurocode>

An exhaustive list of questions to be answered during the registration/randomization procedure is included in the registration check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is registered/randomized.

- ◆ protocol number ?
- ◆ institution number ?
- ◆ callers name ?
- ◆ name of the responsible investigator ?
- ◆ patient's initials (maximum 4 letters) ?
- ◆ patient's chart number (if available) ?
- ◆ patient's birth date (day/month/year) ?
- ◆ performance status at registration
- ◆ eligibility criteria :
  - ◆ all eligibility criteria will be checked;
  - ◆ actual values of the eligibility parameters will be requested when applicable
- ◆ intention to randomize the patient also in the 55012 trial
- ◆ DATE foreseen for TREATMENT START?
- ◆ At the end of the registration/randomization procedure, a number will be allocated to the patient (patient sequential identification number). This number has to be recorded on the registration check-list, along with the date of registration/randomization. The completed check-list must be signed by the responsible investigator and returned to the data center with the initial data of the patient. The sequential identification number attributed to the patient at the end of the registration procedure identifies the patient and must be reported on all case report forms.

## **8. FORMS AND PROCEDURES FOR COLLECTING DATA.**

### **8.1 CASE REPORT FORMS AND SCHEDULE FOR COMPLETION**

Data will be reported on the **EORTC Phase III forms** and sent to:

Livia Giurgea

EORTC Data Center

Avenue Emmanuel Mounier, 83, bte 11

B - 1200 BRUSSELS

Case report forms must be completed according to the following schedule:

### **A. Before the treatment starts.**

The patient must be registered at the Data Center by EuroCODE, INTERNET or by phone (Chapter 7).

The following set of forms has to be returned to the Data Center:

- ◆ Randomization checklist                      Form 0
- ◆ On-study form                                      Form 1
- ◆ QOL-C30 (see chapter 11,  
quality of life assessment)

The optimal way to work is to complete the registration check-list and, if possible, the above set of forms first, and to register the patient through EuroCODE as soon as data are complete; the date of registration and patient sequential identification number are then completed on the check-list, and the whole set can be sent to the Data Center. As soon as the patient has been registered, the first treatment may be administered.

### **B. Immediately after each surgery.**

The following form has to be sent to **ONCOTECH** together with the sample:

- ◆ PATIENT SPECIMEN ONCOTECH  
REQUISITION FORM (see  
instructions in **appendix 1** and on the  
form)

As more than one form could be sent at each surgery, please use one “PATIENT SPECIMEN ONCOTECH REQUISITION FORM” by anatomic site.

P.S. “Primary debulking biopsy form”, “Interval debulking biopsy form”, “Second look biopsy form” have to be completed by ONCOTECH.

### **C. Maximum 4 weeks after each surgery.**

The following set of forms has to be returned to the Data Center:

#### **In case of primary debulking :**

- ◆ Primary debulking form                      Form 2
- ◆ Primary debulking complications form      Form 3

#### **In case of Interval debulking:**

- ◆ Interval debulking form                      Form 6
- ◆ Interval debulking complications form      Form 7

#### **In case of Second look surgery:**

- ◆ Second look form                              Form 9
- ◆ Second look complications form              Form 10



The following form has to be returned to the Data Center :

- E. On the last day of the third chemotherapy cycle and on the last day of the sixth chemotherapy cycle.**

The following form has to be returned to the Data Center:

- ◆ QOL-C30 (see chapter 11, quality of life assessment)

The following forms have to be returned to the Data Center:

- ### G. After treatment discontinuation

**Every 3 months the first 2 years, every 6 months year 3-5, yearly afterwards, the following form has to be returned to the Data Center:**

- ◆ Follow-up form Form 13

**After 6 and 12 months, the following form has to be returned to the Data Center:**

- ◆ QOL-C30 (see chapter 11, quality of life assessment)

The following form has to be returned to the Data Center:

- ◆ First progression form Form 13

The following forms have to be returned to the Data Center:

- ◆ Death form Form 15
- ◆ Follow-up form Form 13

**J. Upon occurrence of a Serious Adverse Event during the treatment period and until 30 days after the end of the last cycle of treatment**

- ◆ a serious adverse event form (form 89) must be completed and faxed to the EORTC Safety Desk according to the procedure described in chapter 9.

**8.2 DATA FLOW**

The case report forms must be completed and signed by the investigator as soon as the requested information is available, according to the above described schedule. It is the responsibility of the investigator to check that all original case report forms have been sent to the Data Center (except the “PATIENT SPECIMEN ONCOTECH REQUISITION FORM which has to be sent to ONCOTECH”) and that they are completely and correctly filled out.

The original copy must be immediately returned to the EORTC Data Center, and a copy must be kept by the investigator.

The EORTC Data Center will perform extensive consistency checks on the CRFs and issue Query Forms in case of inconsistent data. Those Query Forms must be immediately answered and signed by the investigator. The original must be returned to the EORTC Data Center, and a copy must be appended to the investigators copy of the CRFs.

If an investigator needs to bring modifications to a CRF after the original copy has been returned to the EORTC Data Center, he should notify the Data Center in writing (and sign the notification), and append a copy of the notification to his own copy of the CRFs.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form (or a written and signed notification), and the Query Form (or notification) reference is indicated on the CRF.

**9. REPORTING ADVERSE EVENTS**

**Adverse events need only to be reported during the treatment period and until 30 days after the end of the last cycle of treatment**

**(first-line chemotherapy or in relation to primary or interval debulking surgery).**

**9.1 DEFINITIONS**

**Adverse Drug Reactions (ADR)** (*where the product is marketed*) are responses to a drug which are noxious and unintended and which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

**An Adverse Event (AE)** is any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the study medication.

**(‘Responses to a medicinal product’** in the above definitions means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, **i.e. the relationship cannot be ruled out**)

**Serious Adverse Events (SAE) or Serious Adverse Drug Reactions (SADR)** are defined as any undesirable experience occurring to a patient, whether or not considered related to the

investigational drugs or surgical procedure. Adverse events and adverse drug reactions which are considered as serious are those which result in:

- ◆ death
- ◆ a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- ◆ hospitalization or prolongation of hospitalization
- ◆ persistent or significant disability/incapacity
- ◆ a congenital anomaly/birth defect

## 9.2 REPORTING PROCEDURES

### 9.2.1 NON-SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE DRUG REACTIONS

All Adverse Events (AE) and Adverse Drug Reactions (ADR) occurring during the treatment period and until 30 days after the end of the last cycle of treatment will be recorded on the toxicity forms. The investigator will decide if those events are related to the surgery or one of the products used as first-line chemotherapy (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the toxicity forms. Adverse Events (AE) definitely not drug related (i.e. reported as unrelated) will not be considered as adverse drug reactions or toxicity, but reported separately.

The assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after the surgery or of the administration of first-line chemotherapy). There is another reasonable explanation for the event (e.g. the patients clinical condition, other concomittant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the surgery or of the administration of first-line chemotherapy). However, the influence of other factors may have contributed to the event (e.g. the patients clinical condition, other concomittant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

### 9.2.2 SERIOUS ADVERSE EVENTS AND SERIOUS ADVERSE DRUG REACTIONS

All Serious Adverse Events (SAE) and Serious Adverse Drug Reactions (SADR) must be reported to the EORTC safety desk by fax within 24 hours of the initial observation of the event. All details should be documented on the specified Serious Adverse Event/Serious Adverse Drug Reaction Form. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information as described in the “Guidelines for Completing and Reporting Serious Adverse Events/Serious Adverse Drug Reactions.” Initial reports must be followed-up by a complete report within a further 10 calendar days and sent to the EORTC Safety Desk. The Safety Desk will forward all reports within 24 hours of receipt to the trial coordinator and to the Data Manager. In order that regulatory reporting requirements may be met documentation of all reported serious adverse events or serious adverse drug reactions must be completed within 10 calendar days of the initial event.

#### PLEASE SEND THE REPORT TO EORTC SAFETY DESK

**TEL +32 2 774 16 76**

**Fax +32 2 772 80 27**

It should be recognized that Serious Adverse Events (SAE) and Serious Adverse Drug Reactions (SADR) which have not been previously documented, or which occur in a more severe form than anticipated (i.e. they are **unexpected**), are subject to rapid reporting to Regulatory Authorities by the promoter, however, this is not applicable to SAE or SADR which are considered unrelated to the study product whether expected or not. This also applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. The source of the report (investigation, spontaneous, other) should always be specified.

Any serious adverse events which are observed at ANY TIME after the completion of participation in the clinical trial and considered to be possibly related must also be reported to the Safety Desk using the same procedure.

Any questions concerning the reporting of a SAE or a SADR can be asked by phone or E-mail (Safetydesk@EORTC.be). All forms must be dated and signed by the responsible investigator or one of his/her authorized staff member.

## 10. STATISTICAL CONSIDERATIONS

### 10.1 SAMPLE SIZE

The primary endpoint of this study is the overall survival. Group A is considered as the standard arm. Based on earlier EORTC-GCCG experience about 50% of the patients with Stage IIIC or IV disease is optimally debulked and show a median survival of 39 months<sup>9</sup>. (See also “Percentage of optimal debulking under Section 4 .trial design). Based on the EORTC-GCCG interval debulking surgery trial the median survival is in the other patients expected to be 26 months<sup>18</sup>. The median survival of the whole group of patients randomized to Arm A is therefore expected to be 31 months. With an accrual time of 4 years and a minimum follow-up of 3 years, 704 patients are required in order to show equivalence with respect to survival between Arm A and B, with a one-sided type I error of 0.05 and a power of 80%. A hazard ratio larger than 0.8 is regarded equivalent; this corresponds to a median survival of more than 25 months in arm B, if the median survival in arm A is 31 months. According to the expressed interest of the EORTC-GCCG centers and former EORTC-GCCG experience<sup>18</sup>, this number of patients can be accrued in 4 years. At the end of the trial, if no statistical differences are observed between the 2 arms, the preferred treatment will be chosen on the basis of its morbidity or of the quality of life of the patients.

## 10.2 Analysis

- ◆ The analysis will be performed according to the intent to treat policy: all randomized patients will be included in the principal analysis, whatever their eligibility and evaluability status.
- ◆ Overall survival (OS) will be measured from the date of randomization to the date of death, whatever the cause. OS will be estimated in both therapeutic arms by the Kaplan-Meier method. Comparisons will use the log rank test. A confirmatory analysis, stratified by center, will be performed, to take into account eventual differences between surgeons.
- ◆ Progression free survival (PFS) will be measured from the date of randomization to the first documented date of progression, or death, whichever occurs first. PFS will be estimated in both arms by the Kaplan-Meier method. Comparisons will use the log rank test.
- ◆ Treatment complications will be reported in contingency tables; comparisons between therapeutic arms will use the log rank test for trend.

Quality of life will be analyzed according to the methods described in chapter 11.

## 11. QUALITY OF LIFE ASSESSMENT

Given the poor survival rate of patients with ovarian cancer and the toxicity of treatments, quality of life has become an important endpoint in clinical trials. Psychological distress such as symptoms of anxiety and depression, physical impairments, diminished sexual response and relationship concerns are commonly experienced by patients with ovarian cancer<sup>30,31</sup>. One third of ovarian cancer patients being treated with chemotherapy report high levels of psychological distress<sup>30</sup>. Nausea and vomiting, hair loss, peripheral neuropathy, and fatigue are the most prevalent side effects experienced by those patients<sup>31</sup>. In patients with advanced ovarian cancer pain has been reported in approximately 40 % which results in functional impairments in 50 - 66 % of this group<sup>32</sup>.

Debulking surgery and chemotherapy may be associated with substantial side effects and functional impairments. Guidozzi<sup>31</sup> found decreased quality of life among patients with persistent ovarian cancer after surgery and chemotherapy compared with treatment responders. Blythe et al.<sup>33</sup> showed that optimal debulking surgery improved quality of life as measured in terms of continuation of normal activities, employment, confinement to bed, eating regularly, and ability to enjoy life. This study focuses on patients with advanced ovarian carcinoma comparing two different therapeutic strategies. One of the secondary endpoints of this study will be to assess Quality of Life (QOL) benefits in relation to the different therapeutic strategies (arm A versus arm B) and to determine whether the various QOL domains (physical, psychological, social, symptoms) are enhanced by one treatment arm.

### 11.1 QOL MEASUREMENTS

The EORTC core questionnaire QLQ-C30 will be used module to assess the QOL<sup>34</sup>. The EORTC QLQ-C30 addresses physical, psychological and social aspects of QOL. The EORTC QLQ-C30 consists of five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); a global health and a QL scale; six single items concerning appetite loss, constipation, diarrhea, dyspnoea, sleep disturbance, and economic consequences of the disease and treatment. The questionnaire is designed for use in international clinical trials and has been developed in a multicultural setting which facilitates cross study comparisons. Translation for the questionnaire is available in 26 languages.

## **11.2 DATA COLLECTION PROCEDURE**

The EORTC QLQ-C30 will be administered at five points in time (T) in both treatment arms:

T1: before randomization; prior to surgery (arm A), prior to chemotherapy (arm B)

T2: on the last day of the third cycle of chemotherapy

T3: on the last day of the sixth cycle of chemotherapy

T4: 6-months follow-up

T5: 12-months follow-up

The number and frequency of assessment points in both treatment arms are equal. The baseline QOL assessment (T1) allows the comparability of the treatment groups before therapy is initiated. The second and third assessment (T2, T3) will be performed after the third cycle, respectively the sixth cycle of chemotherapy. This timing allows the evaluation of short term treatment effects on QOL, parallel across the trial arms. Two follow-up assessments (6-months T4; 12-months T5) provide long term effect of treatment on QOL in relation to the therapeutic strategies.

For patients who are randomized in both the 55971 and 55012 trials, QOL forms will be collected according to the 55012 schedule only.

T1: within 7 days before randomization

T2: day 1 of the cycle 3 of chemotherapy

T3: day 1 of the cycle 5 of chemotherapy

T4: day 1 of the cycle 7 of chemotherapy

T5: at the end of last cycle

T6: 1<sup>st</sup> year follow up at 3 and 6 months and than stop

Please refer to the 55012 protocol for more details.

## **11.3 PROCEDURE OF DATA COLLECTION**

The questionnaire will be handed out preferably a research assistant (e.g. research nurse) trained in the administration of the QOL instruments. The research assistant will explain the purpose of QOL assessment as well as the handling of the questionnaire and will assist the patient if needed.

Preferably, the patient should complete the questionnaires without conferring with a relative or a member of the staff.

## **12. COST EVALUATION**

Cost evaluation will not be performed in this study.

## **13. DATA MONITORING COMMITTEE**

An Independent Data Monitoring Committee will be appointed to monitor the recruitment rate, the toxicity and the percentage of optimal debulking surgery. If this percentage is substantially different from 50%, the committee may advise to recompute the sample size on the basis of new hypotheses. The toxicity will be reported to the investigators at each half-yearly meeting of the EORTC-Gynecologic Cancer Cooperative Group, according to the standard praxis of the group.

## **14. QUALITY ASSURANCE**

### **Control of data consistency**

Data forms will be entered in the database of the EORTC Data Center by a double data entry procedure. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "on-hold" until resolution of the inconsistencies.

## **15. ETHICAL CONSIDERATIONS**

### **15.1 PATIENT PROTECTION**

The responsible investigators will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments), or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the guidelines for Good Clinical Practice issued by the European Union (See Appendix 5). The protocol will be approved by the EORTC Protocol Review Committee and by the Local, Regional or National Ethical Review Boards.

### **15.2 SUBJECT IDENTIFICATION**

The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patients initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

### **15.3 INFORMED CONSENT**

All patients will be informed of the aims of the study according to the Patient information sheet in Appendix 6, and will consent voluntarily in writing (see appendix 6). Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This must be done in accordance with the national and local regulatory requirements.

## **16. INVESTIGATOR COMMITMENT STATEMENT AND ADMINISTRATIVE RESPONSIBILITIES**

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the Data Center:

- ◆ a commitment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial.

- ◆ a “new commitment form” indicating:
  - ◆ chemotherapy policy for every institution or their intention to include patients in trials 55971 and 55012 and a policy regarding second look operation
  - ◆ obligation to first randomize in 55971 prior to randomize in 55012 (for patients entered in 55971 and 55012)
  - ◆ obligation to complete both CRF (for patients entered in 55971 and 55012) with the exception of the Quality of Life forms. Only Quality of Life forms of the 55012 schedule need to be completed (for patients entered in 55971 and 55012)
  - ◆ obligation to obtain 2 informed consents (for patients entered in 55971 and 55012)
  - ◆ obligation to report a SAE for both trials (for patients entered in 55971 and 55012)
- ◆ notify the local Ethical Committee of the amendments made to the protocol
- ◆ *Reminder: the time planned interval debulking surgery is after 3 courses of chemotherapy.*
- ◆ a copy of the letter of acceptance of the protocol by their local ethical committee
- ◆ a signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared by the commitment form.
- ◆ The name of the responsible surgeons who will perform the surgery for all included patients.
- ◆ The description of the chemotherapy selected for this study (applicable in the 2 treatment arms).
- ◆ the description of the 2nd look policy (applicable in the 2 treatment arms).
- ◆ and, if the following documents are not yet available at the Data Center:
- ◆ their updated Curriculum Vitae
- ◆ the list of the normal ranges, in their own institution, of all laboratory data required by the protocol

As soon as all the documents have been received at the Data Center, the new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial. Patients registration/randomization from centers not (yet) included on the authorization list will not be accepted.

The Study Coordinators (in cooperation with the Data Center) will be responsible for writing the protocol, reviewing all case report forms and documenting their review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

## 16.1 STUDY COORDINATORS:

**Ignace Vergote, MD, PhD,**  
 Department Gynecologic Oncology,  
 University Hospitals Leuven, Gasthuisberg,  
 B-3000 Leuven, Belgium.

Tel.: +32/16/344635

Fax: +32/16/344629

e-mail: Ignace.Vergote@UZ.Kuleuven.ac.be

and,



**Sergio Pecorelli, MD, PhD,**

Department. Gynecologic Oncology,  
Spedali Civili – University of Brescia,  
P. le Spedali Civilli 1,  
25123 Brescia (Italy),

Tel.: 39 30 3995483

Fax. 39 30 3384460

The EORTC Data Center will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Data Center.

## **16.2 EORTC DATA CENTER**

83, avenue Emmanuel Mounier, Bte 11  
B - 1200 BRUSSELS, BELGIUM  
Fax: 32-2-772.35.45

<http://www.eortc.be>

### **Registration of patients:**

Tel.: 32-2-774.16.00

### **Coordinating physician:**

Ivana Teodorovic, MD, MSc  
EORTC Data Center  
Av. E. Mounier 83, box.11  
B 1200 - BRUSSELS

Phone: +32 2 774 16 92

Fax: +32 2 771 38 10

E-mail: [ite@eortc.be](mailto:ite@eortc.be)

### **Statistician:**

Corneel Coens  
Av. E. Mounier 83, box.11  
B 1200 - BRUSSELS

Phone: + 32 2 774 16 32

Fax: + 32 2 771 38 10

E-mail: [cco@eortc.be](mailto:cco@eortc.be)

**Data Manager:**

Livia Giurgea  
EORTC Data Center  
Av. E. Mounier 83, Box 11  
1200 Brussels, Belgium

phone +32 2 774 16 09

fax +32 2 772 35 45

E-mail:ite@eortc.be

All questions concerning membership in the cooperative group should be addressed to the chairman of the EORTC-GCCG:

Ignace Vergote  
Dept Gynecologic Oncology  
University Hospitals Leuven, Gasthuisberg  
B-3000 Leuven Belgium

Tel.: +32/16/344635

Fax: +32/16/344629

e-mail: Ignace.Vergote@UZ.Kuleuven.ac.be

**17. TRIAL SPONSORSHIP/FINANCING**

The Sponsor of the study is the EORTC.

The Director General of the EORTC Central Office/Data Center is:

Professor Françoise Meunier  
EORTC Central Office  
Avenue Mounier 83, Bte 11  
B 1200 - Brussels (Belgium)  
Tel: + 32 2 - 774 16 41  
Fax: + 32 2 - 771 20 04

**18. TRIAL INSURANCE**

The EORTC insurance program covers all patients entered in EORTC studies except patients from USA and Canada.

Insurance within the European Union:

When specific requirements are stated in the national laws of the E.U. countries, the insurance program will take these requirements into account.

For countries where there are no specific requirements, the EORTC provides an insurance coverage which is valid for two years after a patient has completed the treatment strategy being studied by the research protocol. This insurance program covers the EORTC as the promoter, the investigators and all local hospital staff.

Insurance outside the European Union:

The EORTC insurance program only covers claims against the EORTC as the promotor in its role of coordinator of the research and not the investigators and local hospital staff.

## **19. PUBLICATION POLICY**

The final publication of the trial results will be written by the Study Coordinators on the basis of the statistical analysis performed at the EORTC Data Center. The Data Center report will be completed no later than 18 months after the last patient has discontinued therapy. A draft manuscript will be submitted by the study coordinators to the Data Center for review no later than three months after receiving the Data Center report. After revision by the Data Center and other co-authors (according to the statutes of the EORTC-GCCG) the manuscript will be sent to a major scientific journal.

Authors of the manuscript will include the Study Coordinators, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), the Group chairman, and the Data Center data manager and statistician in charge of the trial. All participants and insitutes will be listed in the manuscript.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomized treatment arms may be made publicly available before the recruitment is discontinued.

All publications, abstracts or presentations including data from the present trial will be submitted for review to the EORTC Data Center, the co-authors and the Group Chairman and Secretary at least two weeks prior to submission for abstracts, and four weeks prior to submission of manuscripts and slides for presentation. All data from this study are property of the EORTC-GCCG and the data can not be used without written agreement of the EORTC-GCCG chairman.

**20. ADMINISTRATIVE SIGNATURES****21. LIST OF PARTICIPANTS WITH EXPECTED YEARLY ACCRUAL**

<b>Center</b>	<b>Responsible Physician</b>	<b>Accrual/year</b>
Leuven	Vergote	30
Coimbra	De Oliveira	10-12
Milano (EIO)	Colombo	20-30
Brescia	Pecorelli	30
Antwerp	Vermorken	5-10
Madrid	Mendiola	10-20
Amsterdam (AMC)	K. van der Velden	10-15
Utrecht	Witteveen	10-15
Bristol	Murdoch	5-10
Nottingham	Chan	5-10
Gdansk	Emerich	5-10
Padova	Maggino	8-15
Oslo	Kristensen	10
Oviedo	Lacave	10-12
Rotterdam	van der burg	5-10
Barcelona	Madronal	5-7
Glasgow	Reed	10-15
Torino	Zola	10
<b>TOTAL</b>		<b>198 - 271/year</b>

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## APPENDIX 1. TUMOR SAMPLES FOR BASIC RESEARCH.

The Task Force for Basic Research of the EORTC-GCCG encourages all investigators participating to this study to collect tumor tissue as described below for analyses of different prognostic factors. This study will represent a uniform and large group of patients with advanced ovarian, fallopian tube or peritoneal carcinoma which is ideal for the analyses of the value of new prognostic or predictive variables. In addition, sequential analyses will be able to perform on patients undergoing 2 or 3 surgical procedures during the protocol (primary surgery, interval debulking surgery, and eventual second-look surgery).

Immunohistochemistry on p53, bcl-2, c-erb2, and MIB-1) and DNA flow cytometry have been suggested to be of importance in advanced ovarian carcinoma<sup>35</sup>. Currently several *in vitro* drug response assays have been developed to improve the success of drug(s) selection<sup>36-38</sup>. In particular, the “extreme drug resistance” (EDR) assay has been shown to provide accurate results<sup>39,40</sup>, and will also be tested.

### 1. Site and time points of biopsy.

- 1.1 Site: Preferentially the site of the primary tumor will be sampled. If not possible a biopsy from metastatic sites is allowed.
- 2.2 Time points:
  - Primary debulking surgery.
  - Interval debulking surgery.
  - Second-look surgery.

### 2. Tumor Tissue Procurement and Processing:

- 2.1 Sample Collection: Non-necrotic, sterile tumor specimens of minimum of 0.5 grams (preferably between 1.5 and 3 grams, no more than 5 grams) are obtained by excisional biopsy or core biopsy.
- 2.2 Sample Packaging: All specimen containers, labels and patient identification sheets are provided by Oncotech. Following incisional biopsy, tumor tissue is placed immediately into the sterile culture media tube. This tube is sealed and labeled in smudge-proof ink with the institution number, patient last name, patient first name, patient hospital record number and date of tissue sample collection. The labeled inner tube is then placed into an outer protective tube, which is in turn sealed, placed in the supplied absorbent material, then enclosed in the zip-lock bag provided. The patient identification sheet denoting the study number for the patient is completed. Both the tumor tissue specimen and attached patient identification sheet are enclosed in the cardboard box provided.



### 2.3 Sample Shipment:

On the day of tumor tissue acquisition, immediately after the sample is obtained and packaged, Oncotech is called at +**17145660420** to arrange for Federal Express pick-up. The specimen is to be identified by the referring institution as a protocol sample. Tumor tissue samples must be received and processed by Oncotech within 24 hours of shipment. When it is anticipated that the delay between tumor tissue sample collection and receipt at Oncotech will be more than 24 hours (for samples collected on Saturday or Sunday), the packaged sample must be stored refrigerated (not frozen) until courier pick-up. The phone call for pick-up must then be made on the next business day.

### 3. Tumor Tissue Processing and Assays.

The majority of tumor tissue is disaggregated into single-cell suspension by the Oncotech laboratory. Viability is determined by trypan blue exclusion. Viable cells from the resultant suspension are then exposed to chemotherapeutic agents for the EDR assay. A fraction of untreated tumor tissue is then formalin-fixed/paraffin-embedded for histologic confirmation and immunohistochemical determination of p53, bcl2, MIB1 and c-erb2.

### 4. Final Patient Registration.

Once received at Oncotech, the tumor tissue sample will be assigned a protocol tracking number. Approximately 7 days will be required for sample processing. After successful completion of the EDR, p53, bcl2, MIB1 and c-erb2 assays, the site sending the tumor and one of the Study Coordinators (I. Vergote or S. Pecorelli) will be notified by Oncotech of the results of the assays.

**PATIENT SPECIMEN ONCOTECH REQUISITION FORM**

PRINCIPAL MONITOR  RITA S. MEHTA, M.D.	PRINCIPAL INVESTIGATOR	EORTC Randomization NO. (if available) _ _ _
PROTOCOL NO. EORTC No. 55971	STUDY PERIOD  SCREEN	DATE OF SHIPMENT Day/Month/Year  / /

Hospital _____	City _____
Country _____	Referring Physician _____
Date of Biopsy _____	Birth Day: _____ (dd/mm/yy)
Patient's Initials _____	Hospital I.D. # _____
Type of surgery (Primary, Interval or Second-look Surgery): _____	
Anatomic Site: (Primary tumor or metastatic) _____	

**Instructions for Specimen Handling**

1. Obtain 1-3 grams of fresh viable tumor tissue.
2. Specimens from contaminated sites should be washed with copious amounts of sterile saline.
3. Place tissue immediately in Oncotech Transport Medium.
4. Seal inner and outer vials tightly.
5. Place vials and this form into the shipping package.
6. Close transport package securely and keep refrigerated until courier arrives for pickup.
7. **To arrange for specimen pickup, call Federal Express.**
8. **Notify Oncotech that this specimen for Protocol N° 55971 is on its way**

**Oncotech contact person:**

**Ricardo Parker, email: [rparker@oncotech.com](mailto:rparker@oncotech.com)**  
**Oncotech Incorporated 15501 Red Hill Avenue**  
**Tustin, California 92780**  
**Tel: +17145660420 or +17145660422 if after 4 pm CET**  
**Fax: +17145660421 or +17145660423**

**NOTES:** Do not expose tissue to formalin or other fixatives  
Do not freeze specimen.  
Do not mince specimen.

Oncotech Transport Medium contains growth-supporting factors and antibiotics. **Please refrigerate until use.** Call Oncotech for additional vials of Transport Medium, or to replace out-of-date Transport Medium.

**COMMENTS** (record item number from above for each comment):

SIGNATURE:

**S-1**

## APPENDIX 2. RECOMMENDED CHEMOTHERAPY REGIMENS.

### 1. Paclitaxel -Cisplatinum.

Paclitaxel 135 mg/m<sup>2</sup> over 24 hours, followed by

Cisplatinum 75 mg/m<sup>2</sup>

#### Q 3 WEEKS.

Neutrophils (10 <sup>9</sup> /l)	Platelets (10 <sup>9</sup> /l)	Cisplatinum*	Paclitaxel*
Day 1: > 1.5	Day 1: > 100	100%	100%
Day 1: < 1.5	or, Day 1: < 100	delay 1 week	delay 1 week
Nadir: < 0.5 during 7 d	or, < 25.000	100%	75%
< 0.5 and >38.5°C		100%	75%

\* Percentage of dose of the previous course.

Non-haematological toxicity:

	Cisplatinum*	Paclitaxel*
Neurological NCIC grade >2	stop protocol	stop protocol
Renal creatinine > 1.25 N	stop protocol	stop protocol
Ototoxicity NCIC grade > 2	stop protocol	stop protocol

\* Percentage of dose of the previous course. N: upper normal range

or

Paclitaxel 175 mg/m<sup>2</sup> over 3 hours, followed by

Cisplatinum 75 mg/m<sup>2</sup>

#### Q 3 WEEKS.

Neutrophils (10 <sup>9</sup> /l)	Platelets (10 <sup>9</sup> /l)	Cisplatinum*	Paclitaxel*
Day 1: > 1.5	Day 1: > 100	100%	100%
Day 1: < 1.5	or, Day 1: < 100	delay 1 week	delay 1 week
Nadir: < 0.5 during 7 d	or, < 25.000	100%	75%
< 0.5 and >38.5°C		100%	75%

## Non-haematological toxicity:

	Cisplatinum*	Paclitaxel*
Neurological NCIC grade >2	stop protocol	stop protocol
Renal creatinine > 1.25 N	stop protocol	stop protocol
Ototoxicity NCIC grade > 2	stop protocol	stop protocol

\* Percentage of dose of the previous course. N: upper normal range

2. Paclitaxel - Carboplatinum.

Paclitaxel 175 mg/m<sup>2</sup> over 3 hours, followed by

Carboplatinum AUC 5

**Q 3 WEEKS.**

Neutrophils (10 <sup>9</sup> /l)	Platelets (10 <sup>9</sup> /l)	Carboplatinum*	Paclitaxel*
Day 1: > 1.5	Day 1: > 100	100%	100%
Day 1: < 1.5	or, Day 1: < 100	delay 1 week	delay 1 week
Nadir: < 0.5 during 7 d	or, < 25.000	100%	75%
< 0.5 and >38.5°C		100%	75%

**APPENDIX 3. FIGO STAGING. OVARIAN CANCER <sup>41</sup>.**

The staging is surgical.

STAGE 1 TUMOR LIMITED TO THE OVARIES.

STAGE 2 TUMOR INVOLVING ONE OR BOTH OVARIES WITH PELVIC EXTENSION.

STAGE 3 TUMOR INVOLVING ONE OR BOTH OVARIES WITH INTRAPERITONEAL METASTASES OUTSIDE THE PELVIS AND/OR POSITIVE RETROPERITONEAL LYMPH NODES.

3a. Microscopic disease in the upper abdomen.

3b. Metastases smaller than 2 cm in the upper abdomen.

3c. Metastases larger than 2 cm in the upper abdomen.

Stage 4. Tumor involving one or both ovaries with distant metastases outside the upper abdomen or intrahepatic metastases.

**For cancer of the fallopian tube or peritoneal carcinoam stage 3c or 4 the same rules are followed as for ovarian cancer.**

## APPENDIX 4. SURGICAL GUIDELINES.

Only senior surgeons will be allowed to have the responsibility for the primary, interval or second-look surgery. Each institution will have to appoint their senior surgeons prior to starting the study. Each senior surgeon will follow carefully the guidelines for surgery as mentioned here.

### GUIDELINES FOR PRIMARY AND INTERVAL DEBULKING SURGERY:

- ◆ Both primary debulking and interval debulking surgery will be performed through a **vertical** midline incision.
- ◆ After **opening the abdomen** the abdominal cavity will be evaluated for the presence of tumor and if present for the amount of nodules and largest size of the tumors:
- ◆ The **number** of tumor nodules will be categorized per region (see below) as 0, 1, 2-10, 11-50, or uncountable.
- ◆ The **size** of the tumor nodules will be categorized per region as : 0,  $\leq 10$  mm, 11-20 mm, 21-50 mm, 51 - 100 mm or  $> 100$  mm.
- ◆ An evaluation of size and number of metastases will be done for the **whole abdominal region** and for in addition if possible for **the following regions**:
  1. Diaphragm
  2. Liver surface
  3. Paracolic gutters
  4. Omentum
  5. Intestines
  6. Peritoneal surface (abdominal)
  7. Pelvis (including pouch of Douglas, uterus, bladder, rectum and sigmoid)
  8. Adnexa
  9. Pelvic and para-aortic lymph nodes
  10. Other metastases in the spleen, liver, ... will be recorded separately.
- ◆ Every surgical effort will be made to perform an **optimal cytoreduction**. Optimal cytoreduction is defined as a largest residual tumor mass of  $\leq 1$  cm, but whenever possible the goal of the cytoreduction should be to leave no residual tumor at all. The percentage of patients with “optimal cytoreduction” should be about 50% of the patients randomized to Primary Debulking Surgery.
- ◆ **Bowel** resection or splenectomy is not recommended except when these procedures are necessary to obtain “no residual tumor” at the end of the operation.
- ◆ Specimens preferentially of the primary tumor will be sampled for **basic research** on prognostic factors as stipulated in appendix 2.
- ◆ The surgical management at the time of Debulking Surgery can not be standardized, but the surgeon will be asked to provide a very **precise report** of the procedures performed.
- ◆ At the **end of the operation the number and size** of the residual tumor masses will have to be reported for the whole abdominal cavity and preferentially also for the regions mentioned under “opening the abdomen”.

- ◆ All **early and late complications** (first 4 weeks) of the surgical report will be collected and classified according to the NCIC criteria (see Appendix 7).
- ◆ An **anonimized copy of the surgical report and the pathological report** will be asked for.

## **SECOND-LOOK SURGERY.**

- ◆ Second-look surgery is optional and may be performed with laparoscopy or laparotomy.
- ◆ The same principals apply for second-look surgery as for Primary or Interval Debulking Surgery regarding reporting the number and size of tumor at the start and the end of operation, the need for a precise anonimized surgical report describing the procedures performed, and a the need for pathological report, the sampling of fluid for cytological examination and of tumor tissue for basic research, and the reporting of early and late complications.

## **APPENDIX 5. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**

### **Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th World Medical Assembly  
Helsinki, Finland, June 1964  
and amended by the  
29th World Medical Assembly, Tokyo, Japan, October 1975  
35th World Medical Assembly, Venice, Italy, October 1983  
41st World Medical Assembly, Hong Kong, September 1989  
48th General Assembly, Somerset West, Republic of South Africa, October 1996  
and the  
52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland, October 2000

#### **A. INTRODUCTION**

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.



9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

## **B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

**C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

## **APPENDIX 6. PATIENT INFORMATION - EORTC PROTOCOL 55971.**

You have been asked by your doctor to take part in a clinical trial organized by the European Organization for Research and Treatment of Cancer (EORTC). The following information is meant to help you decide whether or not you wish to take part.

### **Purpose of the study**

You have a malignant disease of the ovary, to be treated by a combination of surgery and chemotherapy. Both treatments have a well established value in the treatment of ovarian cancer. However, the main purpose of this study is to find out what is the best sequence of these 2 treatment modalities. The first possibility (A) is to give first 3 courses of chemotherapy followed by the surgical removal of the tumors in the abdomen, and then again followed by at least 3 courses of chemotherapy. The second possibility (B) is to try to remove the tumors in the abdomen first, then followed by at least 6 courses of chemotherapy, with or without interval debulking surgery. It is the purpose of this study to find out if your chances for definitive cure, for complications of the treatment and for a good quality of life are improved by changing the sequence of the treatment.

### **Side effects**

Surgical removal of the tumors in the abdomen can be complicated with bleeding during or after the operation, infections, bowel disorders,... Both in the treatment possibilities A and B these complications can occur. The side effects of the chemotherapy depend on the type of chemotherapy you will receive. You should ask your doctor about these side effects. The chemotherapy used in A and B is the same.

### **Participation**

To definitively establish which treatment is the best, doctors all over Europe are treating half of the patients according to possibility A and half of the patients according to B. For this reason, chance will decide whether you will receive possibility A or B (randomization) if you decide to participate to this study.

Participation to the trial is totally voluntary and you will be given sufficient time to decide whether or not you wish to take part. A decision not to take part will not affect your relation with your doctor or hospital staff in any way. At any time you are able to refuse further participation in the study. This will not prejudice your subsequent care.

The information regarding your participation in this study will be treated as strictly confidential and will only be used anonymously for the purposes of this trial.

Your doctors will be pleased to answer any further questions you may have.

**Patient informed consent form. EORTC 55971**

Mrs. ....

declares having been informed verbally and in writing on the trial.

The aim of the trial has been explained to me and I hereby declare to be willing to participate voluntarily in the trial.

Place: ..... Date: .....

Signature patient: .....

(An independent witness who records the patient's assent may replace the patient)

Name physician in charge: .....

Place: ..... Date: .....

Signature Physician: .....

For European Union member states, the informed consent procedure must conform to the EU guidelines on Good Clinical Practice. This implies that "consent must be documented either by the subject's dated signature or by the signature of an patient's legally acceptable representative".



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### **Addendum to patient information sheet for trial 55971**

**Clinical trials include only patients who choose to take part.**

**Please take your time to make your decision.**

#### **Title of the research protocol**

“Randomized phase III study comparing upfront debulking surgery versus neo-adjuvant chemotherapy in patients with Stage IIIC or IV epithelial ovarian carcinoma (EORTC 55971)”

#### **Invitation to participate in the study**

The EORTC Gynecological Cooperative Group is initiating a research study on patients that have a disease similar to yours. The study will be conducted at a European level under the supervision of physicians recognized as experts in this field of medicine. Today, you will be invited to take part in this research project after you are given full information about the study. This is a phase III randomized study.

#### **Foreseeable risks and discomforts and methods of drugs administration**

With platinum derivatives, nausea, vomiting, diarrhea, hair loss, tickling in fingers, bone marrow depletion with a decrease in platelets and white blood cells, hearing problems, anaphylactic reactions and fatigue are frequent side effects. With carboplatin, bone marrow depletion, kidney toxicity, hearing problems and tickling in fingers are less pronounced than with cisplatin.

Paclitaxel can give different side effects: allergic reactions, change in blood cell count, tickling in fingers, heart problems, hair loss, unsettled stomach, vomiting, pain in joints and muscles, hearing problems, decreased kidney function. These side effects are common for all patients in the study. Before starting with paclitaxel all patients will receive medication to prevent the allergic reaction. If side effects occur the administration should be withheld until the patient recovers or the dose of the drug will be modified or even stopped. In case of low blood pressure requiring treatment, breathing problems requiring treatment, generalized skin itching, paclitaxel will be discontinued. For other allergic reactions, the paclitaxel infusion may be discontinued at the investigators discretion. Patients will receive adequate treatment and should not re-start in case of a severe allergic reaction.

For the combination regimens with platinum derivatives and paclitaxel the main toxicity is bone marrow depletion, especially leading to decrease in white blood cells. Peripheral neuropathy is rare. Kidney toxicity can occur but is less pronounced when carboplatin is used in this combination.

Nausea and vomiting will be prevented by giving you drugs against vomiting. Hair loss is common, but the hair will grow again after completion of chemotherapy. Bone marrow depression is temporary, is usually of short duration and is usually seen about two weeks after the chemotherapy.

The decrease in white blood cells may increase the risk of infections, a decrease in platelet count (thrombocytopenia) may increase the risk of bleeding.

If neurological toxicity, kidney toxicity or hearing loss, is too high, your treatment will be reassessed.

Cisplatin or carboplatin and Paclitaxel are given as an intravenous infusion. The chemotherapy regimen you will receive, will be chosen by your hospital and this may involve a different combination of drugs.

During this study you are not allowed to breast feed.

## **Description of the research**

### Arm A:

You will first have upfront maximal cytoreductive surgery performed within 3 weeks after the biopsy. This is followed by 3 courses of chemotherapy starting within 3 weeks after the surgery. In patients with non-optimal primary debulking surgery this treatment is followed by interval debulking surgery, which should be performed within 6 weeks after course 3 of chemotherapy in all patients with response or stable disease. This is then followed by at least 3 courses of chemotherapy starting again within 3 weeks after the surgery. A second look surgery is allowed if clinically indicated.

### Arm B:

You will first receive 3 courses of chemotherapy within 3 weeks after the biopsy. Interval debulking surgery should be performed within 6 weeks after course 3 of chemotherapy in all patients with response or stable disease. The surgery will be followed by at least 3 courses of chemotherapy, starting within 3 weeks after the surgery. A second-look surgery is allowed if clinically indicated.

## **Frequency of hospital visits, expected duration of your participation in the trial**

After treatment discontinuation, the frequency of your hospital visits for examination, blood samples, will be every 3 months for the first 2 years, every 6 months for year 3-5, and yearly afterwards. The number of patients to be included in this study is 704 and the duration of recruitment into the study is 4 years.

## **Possible benefits**

There might be less chance of your cancer coming back. You might live longer. The quality of your life might be better. These things cannot be predicted for you. Information from this study might help cancer patients in future.

## **Participation**

Your participation in this research trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. You are free to decide at all times without giving a reason that you no longer wish to participate in the trial. Withdrawal from the trial will not affect your subsequent treatment or relationship with your treating physician or the hospital staff in any way.

Your doctors will be pleased to answer any further questions you may have.

The trial involves the collection of information contained in your medical records and which relates to your disease. It is very important that the information collected is accurate and from time to time it may be checked against your medical records. Duly authorized persons (EORTC staff, national and/or foreign health authority) may have access to your medical records. All information will be

strictly confidential and your identity will never be divulged, you have the right to access this information at any time.

Insurance has been taken by the sponsor of the study according to the current legislation. Everything has been done and will continue to be done to prevent additional health problems occurring as a result of your taking part in this trial.

### **Translational research**

The trial also wishes to involve translational research.

Translational research is research which will be performed on biological samples (such as serum, plasma, tissue,...) that you provide. In this trial biological samples will be tumor tissue removed at the time of your surgery. Translational research will help us to understand prognostic factors, the factors which influence your disease.

These biological samples and data will be treated as confidential as with the rest of data collected for the clinical trial.

This research protocol has been submitted to an ethics committee whose mission is to verify all conditions for your safety and respect of your rights are respected. Approval to this research has been given by the Ethics Committee of \_\_\_\_\_ on \_\_\_\_\_

In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor:

Hospital:

Telephone:

If you consent to join this trial, you will be given a telephone number at the hospital that you can contact at any time if you feel unwell or have further questions. Your family doctor will also be told about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions of your doctor if anything is not clear. You are entitled to keep a copy of this document after you and your doctor have signed it.



**Acceptance of participation**

- ☐ *I have been properly informed of the clinical research that is being proposed to me*
- ☐ *I have received a copy of the patient information sheet (original document + Addendum)*
- ☐ *All my rights have been clearly explained*
- ☐ *I have received a copy of the informed consent document*
- ☐ *"I accept to participate in the research entitled "Randomized phase III study comparing upfront debulking surgery versus neo-adjuvant chemotherapy in patients with Stage IIIc or IV epithelial ovarian carcinoma" and registered under EORTC study number 55971. My participation is completely voluntary and I have the possibility to withdraw my consent at anytime without explanation This will not affect my relationship with my treating physician The data collected on my behalf will be strictly confidential and treated according to the "Directive on Human Protection " and the local applicable laws.*
- My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law".*

Investigator's signature: \_\_\_\_\_ Patient's signature: \_\_\_\_\_

Date: \_\_\_\_\_ Date: \_\_\_\_\_

Person designated by the investigator to participate in the informed consent process

Title/Position: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

## Appendix 7. WHO Performance status.

- 0 Able to carry out normal activity without restriction.
- 1 Restricted in physically strenuous activity but ambulatory and able to do light work.
- 2 Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.
- 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 Completely disabled. Cannot carry out any self-care. Totally confined to bed and chair.

**APPENDIX 8. NCIC TOXICITY CRITERIA.**

<b>ALLERGY</b>					
<b>AL LER Allergy</b>	none	transient rash, fever < 38°C, 100.4°F	urticaria, fever = 38°C, 100.4°F, mild bronchospasm	serum sickness, bronchospasm, req parenteral meds	anaphylaxis
	Fever felt to be caused by <u>drug allergy</u> should be coded as ALLERGY (AL LER). <u>Non allergic</u> drug fever (eg. as from biologics) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to <u>infection</u> , code INFECTION only (IN FEC <u>or</u> IN NEU). NB: Protocols requiring detailed reporting of hypersensitivity reactions, will include a Hypersensitivity Reaction module.				
<b>AL OTH other *</b>	none	mild	moderate	severe	life threatening

BLOOD/BONE MARROW (SI UNITS)						
BL WBC White Blood Count (WBC)	≥ 4.0	10 <sup>9</sup> /l	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
BL PLT Platelets	WNL	10 <sup>9</sup> /l	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
BL HGB Hemoglobin (Hgb)	WNL	g/l	100 - normal	80 - 99	65 - 79	< 65
BL GRA granulocytes (i.e neuts + bands)	≥ 2.0	10 <sup>9</sup> /l	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
BL LYM Lymphocytes	≥ 2.0	10 <sup>9</sup> /l	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
BL HEM Hemorrhage resulting from thrombocytopenia (clinical)	none		mild, no transfusion (includes bruise/hematoma, petechiae)	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
BL OTH Other *	none		mild	moderate	severe	life threatening

CANCER RELATED SYMPTOMS					
<b>CA DEA Death from malignant disease within 30 days of treatment *</b> (grade = 5)	-	-	-	-	-
<b>CA PAI Cancer pain *</b>	none	pain, but no treatment req	pain controlled with non-opioids	pain controlled with opioids	uncontrollable pain
<b>CA SEC Second malignancy *</b>	none	-	-	present	-
<b>CA OTH Other *</b>	none	mild	moderate	severe	life threatening

CARDIOVASCULAR					
<b>CD ART Arterial *</b> (non myocardial)	none	-	-	transient events (eg. transient ischemic attack)	permanent event (eg. cerebral vascular accident)
<b>CD VEN Venous *</b>	none	superficial (excludes IV site reaction → code SK LTO)	deep vein thrombosis not req anticoagulant therapy	deep vein thrombosis req anticoagulant therapy	pulmonary embolism
<b>CD DYS Dysrhythmias</b>	none	asymptomatic, transient, req no therapy	recurrent or persistent, req no therapy	req therapy	req monitoring, or hypotension, or ventricular tachycardia, or fibrillation
<b>CD EDE Edema *</b> (eg. peripheral edema)	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca

<b>CD FUN Function</b>	none	asymptomatic, decline of resting ejection fraction of $\geq 10\%$ but $< 20\%$ of baseline value	asymptomatic, decline of resting ejection fraction by $> 20\%$ of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
<b>CD HBP Hypertension</b>	none or no change	asymptomatic, transient increase by $> 20\text{mm Hg}$ (D) or to $> 150/100$ if previously WNL. No therapy req	recurrent or persistent increase by $> 20\text{mm Hg}$ (D) or to $> 150/100$ if previously WNL. No therapy req	req therapy	hypertensive crisis
<b>CD LBP Hypotension</b>	none or no change	changes req no therapy (incl. transient orthostatic hypotension)	req fluid replacement or other therapy but no hospitalization	req therapy + hospitalization; resolves within 48hrs of stopping agent	req therapy + hospitalization for $> 48\text{hrs}$ after stopping agent
<b>CD ISC Ischemia (myocardial)</b>	none	non-specific T wave flattening	asymptomatic, ST + T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
<b>CD PAI Pain (chest) *</b>	none	pain, but no treatment req	pain controlled with non-opioids	pain controlled with opioids	uncontrollable pain
<b>CD PER Pericardial</b>	none	asymptomatic effusion no intervention req	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion drainage req	tamponade, drainage urgently req; or constrictive pericarditis req surgery
<b>CD TAC Sinus tachycardia *</b>	none	mild	moderate	severe	life threatening
<b>CD OTH Other *</b>	none	mild	moderate	severe	life threatening

COAGULATION					
<b>CG FIB Fibrinogen</b>	WNL	$0.99 - 0.75 \times N$	$0.74 - 0.50 \times N$	$0.49 - 0.25 \times N$	$\leq 0.24 \times N$
<b>CG PT Prothrombin time</b>	WNL	$1.01 - 1.25 \times N$	$1.26 - 1.50 \times N$	$1.51 - 2.00 \times N$	$> 2.00 \times N$
<b>CG PTT Partial thromboplastin time</b>	WNL	$1.01 - 1.66 \times N$	$1.67 - 2.33 \times N$	$2.34 - 3.00 \times N$	$> 3.00 \times N$
<b>CG OTH Other *</b>	none	mild	moderate	severe	life threatening

ENDOCRINE*					
<b>EN AME Amenorrhea</b>	no	irregular menses	≥ 3 months	-	-
<b>EN FLA Hot flashes</b>	none	mild or < 1/day	moderate & ≥ 1/day	frequent & interferes with normal function	-
<b>EN IMP Impotence/Libido</b>	normal	decrease in normal function	-	absence of function	-
<b>EN OTH Other</b>	none	mild	moderate	severe	life threatening

FLU-LIKE SYMPTOMS					
<b>FL FEV fever in absence of infect. * (incl. drug fever)</b>	none	37.1 - 38.0°C 98.7 - 100.4°F	38.1 - 40.0°C 100.5 - 104.0°F	> 40.0°C > 104.0°F for < 24 hrs	> 40.0°C (104.0°F) for > 24 hrs or fever accompanied by hypotension
	Fever felt to be caused by <u>drug allergy</u> should be coded as ALLERGY (AL LER). <u>Non-allergic</u> drug fever (eg. as from biologics) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to <u>infection</u> , code INFECTION only (IN FEC or IN NEU).				
<b>FL HAY Hayfever* (includes sneezing, nasal stuffiness, post-nasal drip)</b>	none	mild	moderate	severe	-
<b>FL JOI Arthralgia* (joint pain)</b>	none	mild	moderate	severe	-
<b>FL LET Lethargy* (fatigue, malaise)</b>	none	mild, fall of 1 level in perf. status	moderate, fall of 2 levels in perf. status	severe, fall of 3 levels in perf. status	-
<b>FL MYA Myalgia* (muscle ache)</b>	none	mild	moderate	severe	-
<b>FL RIG Rigors/Chills* (Gr 3 incl cyanosis)</b>	none	mild or brief	pronounced or /and prolonged	cyanosis	-
<b>FL SWE Sweating* (diaphoresis)</b>	none	mild	moderate	severe	-
<b>FL OTH Other*</b>	none	mild	moderate	severe	life threatening

GASTROINTESTINAL					
<b>GI ANO Anorexia*</b>	none	mild	moderate	severe	dehydration
<b>GI APP Appetite increased*</b>	none	mild	moderate	-	-
<b>GI ASC Ascites (non malignant)*</b>	none	mild	moderate	severe	life threatening
<b>GI DIA Diarrhea</b>	none	increase of 2 - 3 stools per day ; or mild increase of loose watery colostomy output compared to pre-trt	increase of 4 - 6 stools per day, or nocturnal stools; or moderate increase in loose watery colostomy output compared to pre-trt	increase of 7 - 9 stools per day, or incontinence, malabsorption; or severe increase in loose watery colostomy output compared with pre-trt	increase of ≥ 10 stools per day, or grossly bloody diarrhea, or grossly bloody colostomy output or loose watery colostomy output req parenteral support; dehydration
<b>GI DPH Esophagitis/ dysphagia/ odynophagia* (incl recall reaction)</b>	none	dys.or odyn. not req trt, or painless ulcers on esophagoscopy	dys.or odyn. req trt	dys. or odyn. lasting > 14 days despite trt	dys. or odyn. with 10% loss of body wt, dehydration, hosp. req
<b>GI DRY Mouth, nose dryness*</b>	none	mild	moderate	severe	-
<b>GI FIS Fistula* (intestinal, esophageal, rectal)</b>	none	-	-	req intervention	req operation
<b>GI GAS Flatulence*</b>	none	mild	moderate	severe	-
<b>GI HEA Heartburn* (incl. dyspepsia)</b>	none	mild	moderate	severe	-
<b>GI HEM Gastrointestinal bleeding *</b>	none	mild, no transfusion	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive > 4 units transfusion per episode
Bleeding resulting from thrombocytopenia should be coded under BL HEM, not GI					

<b>GI NAU Nausea</b>	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	-
<b>GI OBS Small bowel obstruction*</b>	no	-	intermittent, no intervention	req intervention	req operation
<b>GI PAI Gastrointestinal pain/cramping* (incl. rectal pain)</b>	none	pain, but no treatment req	pain controlled with non-opioids	pain controlled with opioids	uncontrollable pain
<b>GI PRO Proctitis (rectal)</b>	none	perianal itch, hemorrhoids	tenesmus or ulcerations relieved with therapy, anal fissure	tenesmus or ulcerations or other symptoms not relieved with therapy	mucosal necrosis with hemorrhage or other life threatening proctitis
<b>GI STO Stomatitis/ oral</b>	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers, but can eat	painful erythema, edema, or ulcers, and cannot eat	mucosal necrosis and/or req parenteral or enteral support, dehydration
<b>GI TAS Taste, sense of smell altered*</b>	none	mild	moderate	severe	-
<b>GI ULC Gastritis/ulcer*</b>	none	antacid	req vigorous medical management or non-surgical trt	uncontrolled by medical management; req surgery for GI ulceration	perforation or bleeding
<b>GI VOM Vomiting</b>	none	1 episode in 24hrs	2 - 5 episodes in 24hrs	6 - 10 episodes in 24hrs	> 10 episodes in 24hrs or req parenteral support, dehydration
<b>GI OTH Other*</b>	none	mild	moderate	severe	life threatening

GENITO-URINARY					
<b>GU BLA Bladder changes*</b>	none	light epithelial atrophy, or minor telangiectasia	generalized telangiectasia	severe generalized telangiectasia (often with petechiae) or reduction in bladder capacity (< 15 ml)	necrosis, or contracted bladder (capacity < 100 ml), or fibrosis
<b>GU CRE Creatinine</b>	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
<b>GU CYS Cystitis* (non bacterial)</b>	none	mild symptoms, req no intervention	symptoms relieved completely with ther.	symptoms not relieved despite therapy	severe (life threatening) cystitis
	Urinary tract infection should be coded under infection not GU				
<b>GU FIS Fistula* (vaginal, vesicovaginal)</b>	none	-	-	req intervention	req operation
<b>GU FRE Frequency*</b>	none	freq of urination or nocturia twice pre-trt habit	freq of urination or nocturia < hourly	freq with urgency and nocturia ≥ hourly	-
<b>GU HEM Hematuria, bleeding per vagina</b>	negative	micro only	gross, no clots	gross + clots	req transfusion
	Bleeding resulting from thrombocytopenia should be coded under BL HEM not GU.				
<b>GU INC Incontinence*</b>	none	mild	moderate	severe	-
<b>GU OBS Ureteral obstruction*</b>	none	unilateral, no surgery	bilateral, no surgery req	not complete bilateral, but stents, nephrostomy tubes or surgery req	complete bilateral obstruction
<b>GU PAI Genito-urinary pain * (eg : dysuria, dysmenorrhea, dyspareunia)</b>	none	pain, but no treatment req	pain controlled with non-opioids	pain controlled with opioids	uncontrollable pain

<b>GU PRT Proteinuria</b>	no change	1 + or < 0.3 g/% or < 3 g/l	2 - 3 + or 0.3 - 1.0 g/% or 3 - 10 g/l	4 + or > 1.0 g/% or > 10 g/l	nephrotic syndrome
<b>GU VAG Vaginitis* (+/- vaginal discharge) (non-infectious)</b>	none	mild, no trt req	moderate, relieved with trt	severe, not relieved with trt	life threatening
<b>GU OTH Other*</b>	none	mild	moderate	severe	life-threatening

HEPATIC					
<b>HP ALK Alk. Phos or 5'nucleotidase</b>	within normal limits (WNL)	≤ 2.5 x N (Normal)	2.6 - 5.0 x N	5.1-20.0 x N	> 20 x N
<b>HP ALT Transaminase SGPT (ALT)</b>	WNL	≤ 2.5 x N (Normal)	2.6 - 5.0 x N	5.1-20.0 x N	> 20 x N
<b>HP AST Transaminase SGOT (AST)</b>	WNL	≤ 2.5 x N (Normal)	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20 x N
<b>HP BIL Bilirubin</b>	WNL	-	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
<b>HP CLI Liver (clinical)</b>	no change from baseline	-	-	precoma	hepatic coma
<b>HP LDH LDH*</b>	WNL	≤ 2.5 x N (Normal)	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20 x N
<b>HP OTH Other*</b>	none	mild	moderate	severe	life-threatening
	Viral Hepatitis should be coded as infection rather than liver toxicity.				

INFECTION					
<b>IN FEC Infection</b>	none	mild, no active therapy	moderate, localized infection, active therapy req	severe systemic infection, req parenteral trt, specify site	life threatening sepsis, specify site
<b>IN NEU Febrile Neutropenia*</b>	none	-	-	present	-
Absolute granulocyte count $< 1.0 \times 10^9/l$ , fever $\geq 38.5^\circ C$ treated with  (or ought to have been treated with ) IV antibiotics	Fever felt to be caused by <u>drug allergy</u> should be coded as ALLERGY (AL LER). <u>Non-allergy</u> drug fever (eg. as from biologics) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to <u>infection</u> , code INFECTION only (IN FEC <u>or</u> IN NEU).				

METABOLIC (SI UNITS)						
<b>MT AMY Amylase</b>	WNL	$< 1.5 \times N$	$1.5 - 2.0 \times N$	$2.1 - 5.0 \times N$	$> 5.1 \times N$	
<b>MT HCA Hypercalcemia</b>	$< 2.64$ mmol/l	2.64 - 2.88	2.89 - 3.12	3.13 - 3.37	$> 3.37$	
<b>MT LCA Hypocalcemia</b>	$> 2.10$ mmol/l	2.10 - 1.93	1.92 - 1.74	1.73 - 1.51	$\leq 1.50$	
<b>MT HGL Hyperglycemia</b>	$< 6.44$ mmol/l	6.44 - 8.90	8.91 - 13.8	13.9 - 27.8	$> 27.8$ or ketoacidosis	
<b>MT LGL hypoglycemia</b>	$> 3.55$ mmol/l	3.03 - 3.55	2.19 - 3.02	1.66 - 2.18	$< 1.66$	
<b>MT LKA Hypokalemia*</b>	no change or $> 3.5$ mmol/l	3.1 - 3.5	2.6 - 3.0	2.1 - 2.5	$\leq 2.0$	
<b>MT LMA Hypomagnesemia</b>	$> 0.70$ mmol/l	0.70 - 0.58	0.57 - 0.38	0.37 - 0.30	$\leq 0.29$	
<b>MT LNA Hyponatremia*</b>	no change or $> 135$ mmol/l	131 - 135	126 - 130	121 - 125	$\leq 120$	
<b>MT OTH Other*</b>	none	mild	moderate	severe	life threatening	



NEUROLOGIC					
<b>NE CER Cerebellar</b>	none	slight incoordination, dysdiadochokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
<b>NE CON Constipation</b>	none or no change	mild	moderate	severe, obstipation	ileus > 96 hrs
<b>NE COR Cortical (includes drowsiness)</b>	none	mild somnolence	moderate somnolence	severe somnolence, confusion, disorientation, hallucinations	coma, seizures, toxic psychosis
<b>NE DIZ Dizziness* (includes lightheadedness)</b>	none	mild	moderate	severe (includes fainting)	-
<b>NE EXT Extrapyramidal/ Involuntary movement*</b>	none	mild agitation (includes restlessness)	moderate agitation	torticollis, oculogyric crisis, severe agitation	-
<b>NE HED Headache</b>	none	mild	moderate or severe but transient	unrelenting and severe	-
<b>NE HER Altered hearing</b>	none or no change	asymptomatic hearing loss on audiometry only	tinnitus, symptomatic hearing changes not req hearing aid or trt	hearing loss interfering with function but correctable with hearing aid or trt	hearing changes or deafness not correctable
<b>NE INS Insomnia*</b>	none	mild	moderate	severe	-
<b>NE MOO Mood</b>	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
<b>NE MOT Motor</b>	none or no change	subjective weakness, no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
<b>NE PAI Neurologic pain* (eg : jaw pain)</b>	none	pain, but no treatment req	pain controlled with non-opioids	pain controlled with opioids	uncontrollable pain
<b>NE PER Personality change*</b>	no change	change, not disruptive to patient or family	disruptive to patient or family	harmful to others or self	psychosis
<b>NE SEN Sensory</b>	none or no change	mild paresthesias, loss of deep tendon reflexes (including tingling)	mild or moderate objective sensory loss, moderate paresthesias	sensory loss or paresthesias that interfere with function	-
<b>NE VIS Vision</b>	none or no change	blurred vision	-	symptomatic subtotal loss of vision	blindness
<b>NE OTH Other* (includes pain)</b>	none	mild	moderate	severe	life-threatening
	Code <u>chest pain</u> CD PAI, <u>muscle aches</u> (myalgia) FL MYA, <u>abdominal pain</u> GI PAI, and <u>local pain</u> at IV site SK LTO. For all other types of pain (eg. bone pain), code NE OTH.				

PULMONARY					
<b>PU COU Cough*</b>	none	mild	moderate	severe	-
<b>PU EDE Pulmonary edema*</b>	none	-	out-patient management	in-patient management	req intubation
<b>PU EFF Pleural effusion* (non-malignant)</b>	none	mild	moderate	severe	life threatening
<b>PU FIB Pulmonary fibrosis*</b>	normal	radiographic changes, no symptoms	-	changes with symptoms	-
<b>PU HEM Hemoptysis*</b>	none	mild, no transfusion	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
	Bleeding resulting from thrombocytopenia should be coded under BL HEM, not PU				
<b>PU PAI Pulmonary pain*</b>	none	pain , but not treatment req	pain controlled with non-opioids	pain controlled with opioids	uncontrollable pain
<b>PU PNE Pneumonitis* (non-infectious)</b>	normal	radiographic changes, symptoms do not req steroids	steroids req	oxygen req	req assisted ventilation
<b>PU SOB Shortness of breath (dyspnea) (incl wheezing)</b>	none or no change	asymptomatic, with abnormality in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity, apnea without cyanosis	dyspnea at rest, apnea with cyanosis
<b>PU VOI Voice changes* (incl. hoarseness, loss of voice)</b>	none	mild	moderate	severe	-
<b>PU OTH Other*</b>	none	mild	moderate	severe	life-threatening
	Pneumonia should be considered infection and not graded as pulmonary toxicity unless felt to be resultant from pulmonary changes directly induced by treatment				

SKIN					
<b>SK ALO Alopecia</b>	no loss	mild hair loss	pronounced or total head hair loss	total body hair loss	-
<b>SK CHA Skin changes* (eg. photosensitivity)</b>	none	localized pigmentation changes	generalized pigmentation changes or atrophy	subcut.fibrosis or localized shallow ulceration	generalized ulcerations or necrosis
<b>SK DES Desquamation*</b>	none	dry desquamation	moist desquamation	confluent moist desquamation	-
<b>SK DRY Dry skin*</b>	none	mild	moderate	severe	-
<b>SK FAC Flushing* (eg: -facial)</b>	none	mild	moderate	severe	-
<b>SK HEM Bruising/bleeding</b>	none	mild, no transfusion	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
	Bleeding from thrombocytopenia should be coded under BL HEM, not SK				
<b>SK LTO Local toxicity (reaction at IV site)</b>	none	pain	pain and swelling, with inflammation or phlebitis	ulceration	plastic surgery indicated

<b>SK NAI Nail changes*</b>	none	mild	moderate	severe	-
<b>SK PAI Skin pain* (include sclap pain)</b>	none	pain, but no treatment req	pain controlled with non-opioids	pain controlled with opioids	uncontrollable pain
<b>SK RAS Rash/Itch* (not due to allergy) (includes recall reaction)</b>	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoma	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
<b>SK OTH Other*</b>	none	mild	moderate	severe	life threatening

WEIGHT					
WT GAI Weight Gain	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	≥ 20.0%	-
WT LOS Weight Loss	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	≥ 20.0%	-

OTHER					
OT OTH Other*	none	mild	moderate	severe	life-threatening
	For toxicity which do not have an existing code, but do fit into an existing toxicity category, use "other" variable in the appropriate toxicity category (eg. code sinus tachycardia CARDIOVASCULAR OTHER (CD OTH). Only toxicities which <u>do not fit into existing categories</u> should be coded OTHER OTHER (OT OTH).				